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The Journal of Pediatrics

VOL. 9 JULY, 1936 NO. 1

Original Communications

THE EFFECT OF VITAMIN D ON LINEAR GROWTH IN INFANCY

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VERVA VANDECAR, R.N.
IOWA CITY, IOWA

THE influence of improved nutrition and environment on the rate of growth of school children has often been noted. Baldwin,[1] among others, demonstrated that children from better class homes grow at faster than the average rate. The more rapid growth was credited to better nutrition. His findings have been amply confirmed.[2] More recently increased rates of growth of average European school children have been reported[3] and the cause ascribed not only to diet, but also and to a greater degree to the increase in outdoor life and greater exposure of the body to sunlight.

In contrast to the numerous studies of growth of school children, the literature contains few reports concerning the effect of modern dietaries and mode of life on the rate of growth during infancy. Robertson[4] in 1916 compared the rate of growth of breast-fed British infants in England and in Australia, and considered the increased rate of growth of the Australian born infants as due to improved "environment." Sunlight certainly would be one of the most important environmental factors to be considered. Daniels and her associates[5] first pointed out that well infants given cod liver oil grow at a greater rate than infants similarly fed except that no cod liver oil was given. The increased growth was credited primarily to the greater vitamin D intake, and the conclusion was drawn that accepted standards of growth were too low. Both of the above studies concerned growth in weight only. Nelson[6] reported from this laboratory that infants given acidified whole milk feedings and ingesting one teaspoonful of cod liver oil daily were both longer and heavier than the accepted standards for their ages.

From the Department of Pediatrics, State University of Iowa.
This study was assisted by a grant from Mead Johnson and Company, Evansville, Indiana.

The average increase in length of well male infants during the first year of life has been variously given as from 19.8 (Quetelet[7]) to 25 cm. (von Pirquet[8]). Baldwin[9] in 1921, from a study of nearly 5,000 Iowa male infants, stated that the average Iowa male infant grows from 52.4 cm. at birth to 74.7 cm. at one year of age and that American infants were superior to French and German infants in height and weight during infancy. A length increase of 22 cm. during the first year of life is still a common standard for American male infants.[10]

During each of the past seven years a group of well male infants has been housed in our metabolism ward, particularly for the study of mineral metabolism. Careful records of growth and development have been kept, as well as the usual ward records. The type of feeding has remained practically constant, namely, cow's milk acidified or otherwise curded and with 6 per cent added carbohydrate, usually a dry dextrin-maltose preparation. Each infant has been given 30 c.c. of orange juice daily up to three months of age, and 60 c.c. daily subsequently. Sieved vegetables were included in the diet at five months of age, and sieved fruits at six months. For this group of studies, cereal was not included during the period discussed. When the vitamin D intake was unrestricted, an egg yolk a day was given to infants over four months of age. For infants whose vitamin D intakes were to be limited, ferric citrate solution was given instead of the egg.

It became obvious during the first year's study in 1930 that the rate of growth of each infant observed[11] exceeded the average rate of growth of Iowa infants as reported by Baldwin. A search was made for higher standards, and those published in 1929 by Kornfeld[12] were chosen. These standards were based on studies of American, British, and North and Central European infants—racial stocks prevalent in our own groups. While the Kornfeld standard rate of growth was greater than the Baldwin standard, the infants studied by us grew in length at a rate definitely more rapid than the Kornfeld standard rate, and maintained weights normal for their lengths according to that standard. This growth was achieved despite an epidemic of acute respiratory infection occurring during the study.

During the following three years, the groups of infants studied also showed the same increase in rate of growth as was observed in 1930. In the study of 1934 the intake of vitamin D was decreased from approximately 340 U.S.P. units daily to the amount which could be consumed by a baby given irradiated milk, namely, from 60 to 135 U.S.P. units daily. The intake of vitamin A was also decreased by this procedure. The infants of this study grew at almost exactly the standard (Kornfeld) rate of growth, although the other factors of the diet and care were the same as during the preceding years. At the close of the study in the spring the infants were put out in the sun, fully clothed, during a part of each sunny day. The rate of growth increased. Cod liver oil was

then given in the amount of one teaspoonful daily, and the growth of the younger infants quickly attained the ward average. The two older infants showed increased growth, but not at the same rate as did the younger infants.

The following year the vitamin D intake of the group studied was obtained from milk containing a cod liver oil concentrate in the amount of 400 U.S.P. units to the quart (from 245 to 400 units ingested daily), or from 400 U.S.P. units daily as cod liver oil. The intakes of both vitamins D and A were thus increased, and again the growth rate of the infants increased above the Kornfeld standard. During the past year four infants have been given irradiated milk feedings permitting a vitamin D intake of 60 to 135 U.S.P. units daily and have maintained only an average rate of growth. The growth results obtained are thus readily duplicated by repetition of conditions.

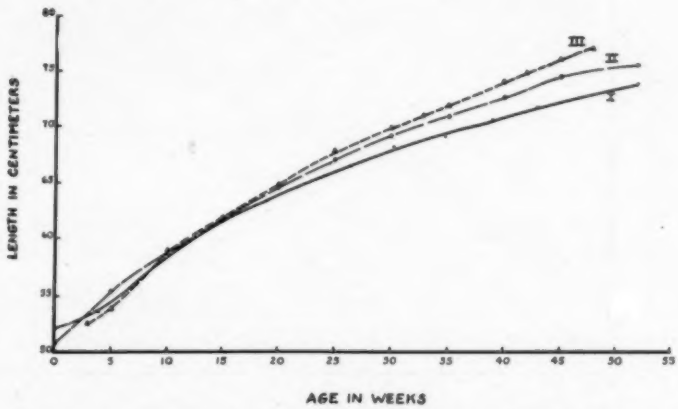

Chart 1.—*I*, average rate of linear growth of Iowa male infants, Baldwin, 1921. *II*, average rate of linear growth of male infants, Kornfeld, 1929. *III*, average rate of linear growth of thirty-six male infants given whole milk feedings and 340 U.S.P. units of vitamin D as cod liver oil daily.

The results of the seven years' observations are shown in the charts. The three curves of Chart 1 are: *I*, the average growth rate of Iowa infants as reported by Baldwin in 1921; *II*, the average rate of growth according to Kornfeld's standards of 1929; and *III*, the average rate of growth of thirty-six infants given the equivalent of one teaspoonful of cod liver oil daily (340 to 400 U.S.P. units of vitamin D). The average length of the infants whose growth is shown in Curve *III* was 0.5 cm. less than that of the other two groups at three weeks of age, but by the forty-eighth week this group averaged 77 cm. in length, in contrast to 75 cm. for the Kornfeld standard and 73 cm. for the Baldwin standard. The average rate of growth of the two groups of infants fed irradiated milk or its vitamin D equivalent (60 to 135 U.S.P. units of vitamin D daily) is almost identical with that of Curve *II*, faster than the growth

of the average Iowa infant of 1921, but slower than that of the infants given the equivalent of a teaspoonful of cod liver oil. For purposes of comparison it may be stated that the standards recently reported by Stuart[13] for the growth of Boston infants are also nearly identical with the Kornfeld standard.

Chart 2 includes the same growth Curve *III* as is shown in Chart 1, namely, the rate of growth of infants given 340 or more U.S.P. units of vitamin D as cod liver oil daily (who will hereafter be designated as the high vitamin D group). The shaded portion and the light background lines indicate the average range and the normal limits, respectively, of the Kornfeld standard. Curves *I* and *II* show the average rates of growth of the two groups given a moderate amount of vitamin

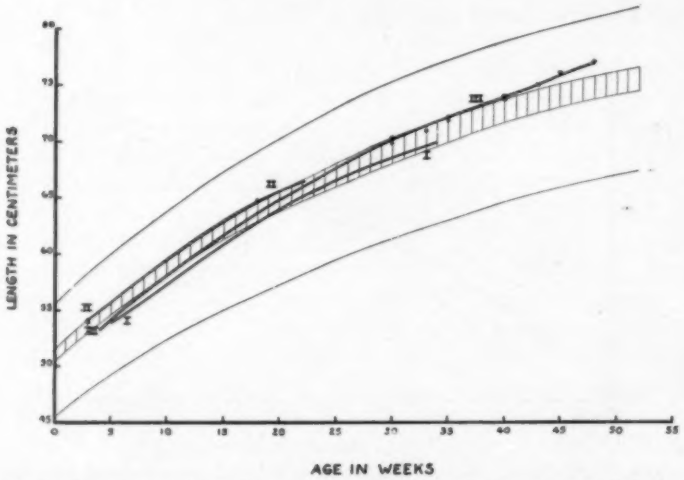

Chart 2.—*I*, average rate of linear growth of seven infants given irradiated milk or its vitamin D equivalent as cod liver oil or cod liver oil concentrate milk, ingesting from 60 to 135 U.S.P. units of vitamin D daily.

II, average rate of linear growth of four infants given irradiated milk (60 to 135 U.S.P. units of vitamin D daily).

III, same curve as *III*, Chart 1. In this and succeeding charts, the shaded portion and the light background lines indicate the average range and normal limits respectively of the Kornfeld standard.

D as irradiated milk (135 U.S.P. units to the quart) or its vitamin D equivalent in either cod liver oil or cod liver oil concentrate milk. The infants of Group II were larger at the beginning of the study than the infants of Group I. The infants of Group I were born in the winter, those of Group II in late summer. Curve *I* follows closely the lower line of the Kornfeld average range, and Curve *II* follows the upper line as closely. Both of these groups, therefore, may be considered as growing at the standard rate.

The infants of Group II, who were given irradiated milk as the only source of vitamin D, received from 60 to 135 U.S.P. units of vitamin

D daily and no additional vitamin A. The infants of Group I each received irradiated milk for from six to eight weeks of the study, and during the remainder of the period received the vitamin D equivalent as cod liver oil or cod liver oil concentrate milk, both of which provide additional vitamin A. These infants, therefore, during two-thirds of the study were receiving more vitamin A than the infants of Group II. The differences in growth rates between Group I and II are negligible. This indicates that vitamin D rather than vitamin A was the factor responsible for the increase in growth rate in Group III.

It seems logical to assume that in this study vitamin D is the chief factor affecting the rate of linear growth, for growth in length depends primarily on skeletal growth, and vitamin D, through its effect on mineral retentions, increases the amount of calcium salts available for

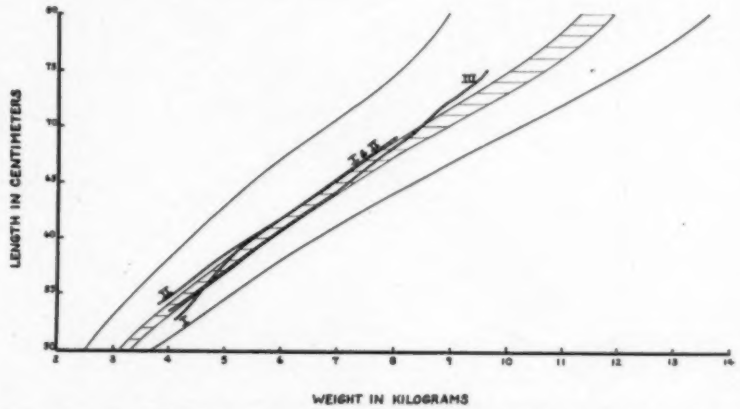

Chart 3.—Weight-length curves for the three groups of infants whose growth in length was shown in Chart 2.

The shaded portion and fine lines indicate the average range and normal limits of the Kornfeld weight-length standard.

the formation of new bone. Supporting this assumption is the fact that, although the milk intakes were the same in the three groups, the average quantities of calcium and phosphorus actually retained daily by the infants given one teaspoonful of cod liver oil a day were significantly greater than the mean daily retentions of calcium and phosphorus by infants given the moderate intake of vitamin D (135 unit milk).[14] The rate of growth of the group given high vitamin D (Curve *III*) was consistently greater throughout the entire period studied. At the beginning of the study, the infants of Group III were the same average size as those of Group I and 1.75 cm. shorter than the infants of Group II. At twenty-two weeks of age, the infants of Group III averaged only 0.5 cm. shorter than those of Group II and were more than 1 cm. longer than the infants of Group I. By thirty-four weeks of age, the difference

between the growth rates of Groups I and III was more marked, as the growth rate of Group I showed a distinct slowing, while that of Group III continued to increase, making a difference of nearly 2 cm. in the average length of the two groups. At forty-eight weeks, the average length of the infants in Group III was 77 cm., 3.5 cm. greater than that expected from their size at the beginning of the study according to the Kornfeld standard.

The weight-length curves for these three groups of infants are shown in Chart 3. The shaded portions and fine lines again represent the average range and normal limits of the Kornfeld standards, and the curves are numbered as in Chart 2. It will be observed that the infants of all three groups tend to become somewhat slender but remain close to the average range.

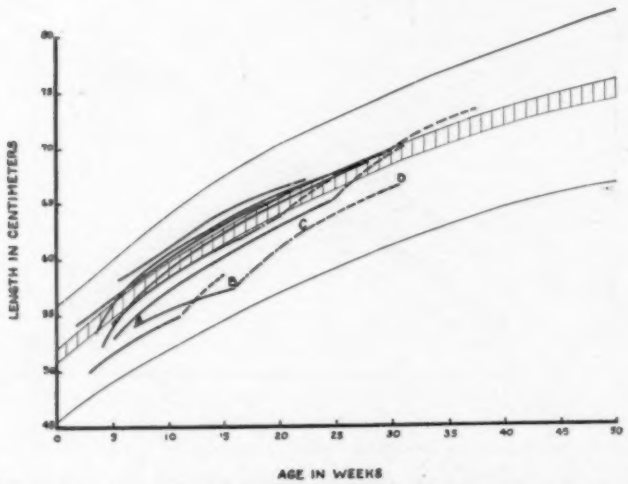

Chart 4.—Growth in length curves of individual infants with moderate vitamin D intake (60 to 135 U.S.P. units of vitamin D daily). Standards shown as in Chart 2.

Dot-dash lines indicate periods when infants received sunlight in addition to diet; broken lines indicate periods when both sunlight and cod liver oil were given.

Chart 4 depicts eight curves of growth in length of individual infants of the two groups given the moderate amount of vitamin D (60 to 135 U.S.P. units). The shaded portions and light lines indicate the average range and normal limits of the Kornfeld standard, as in Chart 2. The growth rate of a very short infant is compared with the slope of the lowest line of the standard range; that of a very tall infant with the uppermost standard line; the slope of the growth curves of the remainder is compared with that of the central average range. In this manner average rates are not biased by comparing the rate of growth of very large or very small infants with that of infants average in size at the beginning of the study. It will be observed that in general the growth

curves of all the infants fed a moderate amount of vitamin D tend to parallel the lines of the standard. Two infants showed a greater than standard growth during early infancy, but by the tenth week of age the growth rate of both had definitely slowed. Growth of infants during the first weeks of life probably may be affected by the vitamin D intake of the mothers during the latter part of pregnancy.

The dot-dash lines of the growth curves indicate the periods during which the infant received additional sunlight, and the broken lines the periods when both sunlight and additional cod liver oil were given. For example, the line *AB* represents the growth of one infant given milk containing 135 U.S.P. units of vitamin D to the quart; *BC*, his growth on the same diet plus the added effect of sunlight; *CD*, the effect of one

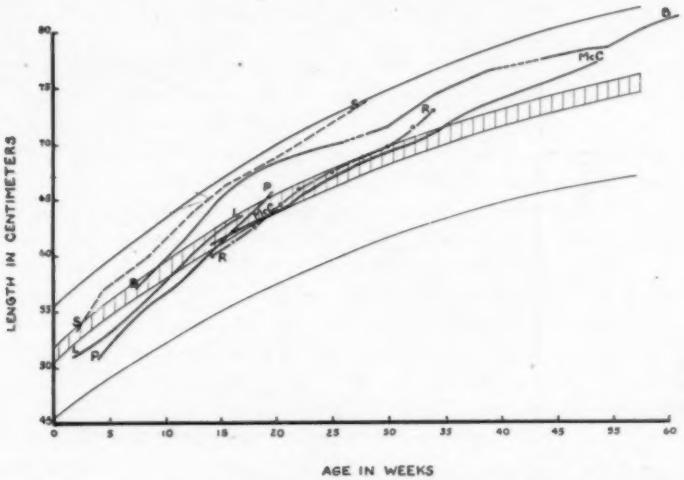

Chart 5.—Linear growth curves of individual infants given 340 U.S.P. units of vitamin D daily. Curve *S*, the growth rate of a breast-fed infant given 340 units of vitamin D daily; on curve *B*, the dotted portions show periods of illness.

teaspoonful of cod liver oil daily added to the regimen of the preceding period. This curve gives further evidence that for these babies vitamin D rather than vitamin A was the important factor and that probably the vitamin A ingestion was already adequate for growth without further additions.

Chart 5 records, in the same manner as Chart 4, the individual growth curves of infants given one teaspoonful of cod liver oil daily (340 or more U.S.P. units of vitamin D). These growth rates are typical of the group and were chosen to illustrate particularly the rates of growth of infants both small and large at the beginning of the study. The dotted curve *S* represents the growth rate of a baby kept under the same housing conditions as the others, but fed human milk and one teaspoonful of cod liver oil daily. This curve is not included in the averages,

but it is shown here to illustrate the fact that more rapid growth is observed also with other types of feeding when the vitamin D intake is high. Curve *B* is of particular interest because it shows the effect of illness on the growth rate of an infant. This child, the fifth in the family, was of Scandinavian stock and was born of a mother with nephritis. He entered the ward at seven and one-half weeks of age and was of average length and weight. The infant was always unusually susceptible to respiratory infection. Minor respiratory infections are not noted on the growth curve. The first dotted portion of the curve denotes the period of a mild chickenpox infection, and the second dotted portion illustrates the effect of a severe illness, a laryngitis requiring tracheotomy, wherein the child was critically ill for a period of several days and moderately ill for a month or more. The growth rate was

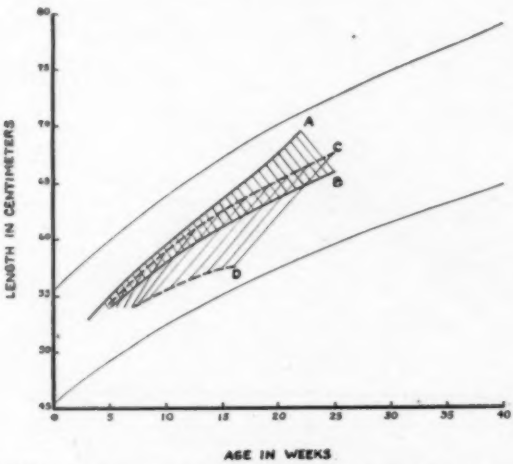

Chart 6.—Relative variability of growth rates with different intakes of vitamin D. The shaded portion between the two solid lines represents the range of growth rates exhibited by thirty-six infants given 340 units of vitamin D daily as cod liver oil; the portion between the two dotted lines, the range of growth rates shown by eleven infants given 60 to 135 units of vitamin D daily, as cod liver oil, cod liver oil concentrate milk, or irradiated milk.

definitely slowed for a period of nearly ten weeks, but later compensated by a rapid increase during the succeeding seven weeks. At seven weeks of age this baby was average in height, while at one year of age he was 5 cm. taller than the expected height by the Kornfeld standard, notwithstanding one severe and several minor illnesses. The remaining curves illustrate the rates of growth customarily observed with the dietary regimen used, namely, whole milk feedings and one teaspoonful of cod liver oil daily.

In Chart 6 are indicated the relative variability of growth rates that may be expected from the two dietary regimens under discussion, namely, moderate and high vitamin D. The shaded portion between the two

solid lines represents the difference in growth rate, respectively, of the group given the larger amount of vitamin D (340 U.S.P. units daily); the portion between the two dotted curves represents similarly the range of growth rate among the infants given the moderate amount of vitamin D (135 unit milk or its equivalent).

The range in the group given the smaller amount of vitamin D is almost double that in the high vitamin D group, although the former group included less than half as many children as the latter. For convenience in comparison, the increases in length between seven and sixteen weeks and between sixteen and twenty-two weeks of age are stated. The most rapid growth from seven to sixteen weeks of age in the high vitamin D group was 7.4 cm., the slowest 6.1 cm., a difference of 21 per cent. The moderate vitamin D group varied from 6.8 to 3.5 cm. increase in length, a 94 per cent range. Between sixteen and twenty-two weeks of age the rate of growth slows in both groups. The most rapid growth in the moderate vitamin D group just equalled the slowest growth in the high vitamin D group, namely, 3 cm. The most rapid growth in the high vitamin D group was 5.3 cm.

Much discussion has been presented in the literature on the general subject of desirability of rapid or slow growth.[15] It seems to be customary to consider as normal whatever happens to be the prevailing rate. However, when one considers that the customs of modern life necessarily deprive the infant of sunlight and that the ingestion of cod liver oil or other source of vitamin D tends to bring the environment back to its original normal, it would seem that the rate of growth illustrated by the high vitamin D group is nearer the true normal than would be the growth of infants not so fed. The fact that the breast-fed baby, close-housed but given cod liver oil, grew at the same rapid rate may be taken as evidence in this direction.

The increased rates of growth of the Kornfeld and the Stuart standards over the earlier standards may readily be due to increased intake of vitamin D or exposure to sunlight, even though such alterations in regimen may have been casual. At the time when the Baldwin standards were prepared, it was not customary to give cod liver oil to well infants, and babies were more often shielded from sunlight than exposed to it. Since 1920 customs have altered materially in this regard. Standards compiled recently may include all grades of vitamin D (and A) intake, the resultant being a definite increase in growth rate, but not equal to the average growth rate when each infant studied receives ample cod liver oil.

SUMMARY

The rate of growth in length of infants given one teaspoonful of high grade cod liver oil (340 to 400 U.S.P. units of vitamin D daily) has been compared with the rate of linear growth of infants given the same type of diet, but with the source of vitamin D from irradiated milk

(60 to 135 U.S.P. units of vitamin D daily) or its vitamin D equivalent as cod liver oil or cod liver oil concentrate milk, and with standard growth rates reported in the literature.

A review of the growth standards shows that the rate of linear growth in infancy is increasing. Standards reported in 1929 and 1933 show rates of growth definitely increased over those of older standards.

Infants given 340 to 400 U.S.P. units of vitamin D daily grow at rates definitely more rapid than those of even the recent standards. Infants ingesting from 60 to 135 U.S.P. units of vitamin D daily grow at the same rate as the recent standards. Exposure to sunlight increased the rate of growth in the few infants in whom this measure was tried and who were receiving the lower of the two stated amounts of vitamin D.

The increased rate of linear growth is ascribed chiefly to the increased intake of vitamin D and its resultant effect on skeletal growth. Although the influence of vitamin A has not been entirely excluded, certain of the observations recorded indicate that vitamin A was not the limiting factor in the growth of the infants studied.

REFERENCES

1. Baldwin, B. T.: Physical Growth and School Progress, U. S. Bureau of Education, 1914, No. 10, Washington.
2. Gray, H.: Am. J. Dis. Child. **32**: 554, 1926.
3. Kornfeld, W.: Wien. klin. Wchnschr. **46**: 683, 1933.
   Koch, E. W.: Arch. f. soziale Hyg. u. Demeg **6**: 385, 1933-34 (abst. in Nutrition Abst. and Rev. **5**: 175, 1935).
4. Robertson, T. B.: Am. J. Physiol. **41**: 535, 1916.
5. Daniels, A. L., Hutton, M. K., Stearns, G., and Hejinian, L.: Am. J. Dis. Child. **37**: 1177, 1929.
6. Nelson, M. V.: Ibid. **39**: 701, 1930.
7. Quetelet: Quoted by Czerny-Keller, Des Kindes Ernährung, Leipzig, 1925, Franz Deuticke.
8. Von Pirquet, C.: Ztschr. f. Kinderh. **6**: 253, 1913.
9. Baldwin, B. T.: Physical Growth of Children, Birth to Maturity, University of Iowa Studies, Iowa City, 1921.
10. Holt, L. E., Jr., and McIntosh, R.: Diseases of Infancy and Childhood, ed. 10, New York, 1933, D. Appleton & Co.
11. Jeans, P. C., and Stearns, G.: Am. J. Dis. Child. **46**: 69, 1933.
12. Kornfeld, W.: Ztschr. f. Kinderh. **48**: 188, 1929-30.
13. Stuart, H. C.: J. PEDIAT. **5**: 194, 1934.
14. Jeans, P. C., and Stearns, G.: Proc. Soc. Exper. Biol. & Med. **31**: 1159, 1934; **32**: 1464, 1935.
    Stearns, G., and Jeans, P. C.: Proc. Am. Soc. Biol. Chem. **114**: c, 1936.
15. Wetzel, N. C.: J. PEDIAT. **4**: 465, 1934.
    Editorial, J. A. M. A. **104**: 1826, 1935.
    Sherman, H. C., and Booher, L. E.: J. Biol. Chem. **93**: 93, 1931.
    Campbell, H. L., Bessey, O. A., and Sherman, H. C.: J. Biol. Chem. **110**: 703, 1935.

THE PREMATURE INFANT

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THIS study supplements the recent publication on institutional mortality of the newborn infant[1] and deals with the care and vital statistics of 752 premature infants in 10,660 consecutive births. Comparisons with similar data, published from other clinics, have been made on the basis of weight since this one measurement is at present the only uniform criterion of prematurity. In recent literature,[2, 3] specialized procedures have been stressed, which are of undoubted value in the care of premature infants but are beyond the reach of many clinicians. The data reported in this study are intended to show the results obtainable with readily available and simple measures.

In Table I the distribution of the 752 premature infants from the 10,660 consecutive births is shown according to three criteria: body weight, crown-to-heel length, and period of gestation. The 97 infants over 2,500 grams at birth have been included since they are considered by two of these three criteria to be prematurely born.[1] The 47 infants in the fourth group have been included for purposes of comparison with data using weight as the only criterion of prematurity.

TABLE I

CLASSIFICATION OF 752* PREMATURE INFANTS IN 10,660 CONSECUTIVE BIRTHS

WT. IN GM. AT BIRTH	CROWN-HEEL LENGTH 47 CM. AND UNDER		CROWN-HEEL LENGTH OVER 47 CM.		TOTAL
	GESTATION 37 WK. AND UNDER	GESTATION OVER 37 WK.	GESTATION 37 WK. AND UNDER	GESTATION OVER 37 WK.	
1,000 and under	31				31
1,001 to 1,500	51				51
1,501 to 2,000	141	13	1		155
2,001 to 2,500	179	166	26	47	418
2,501 to 2,800	97				97
Total	499	179	27	47	752

*Fourteen premature infants were not included in this total since they were discharged to other institutions, eleven of the fourteen going to the Century of Progress.

In Table II are shown data from two clinics with respect to (1) the average initial weight loss, (2) the average time required to regain this weight loss, and (3) the average length of stay in the hospital. These findings are compared on the basis of weight. The data from the 752

From the Chicago Lying-In Hospital and the Departments of Obstetrics and Gynecology and the Department of Pediatrics, University of Chicago.

premature infants appear to show that a very small infant may regain birth weight in as short a time as the one born near term.

TABLE II

COMPARATIVE STATISTICS FROM PREMATURE STATIONS

	CHICAGO LYING-IN HOSPITAL*					SARAH MORRIS HOSPITAL†				
	NO. OF IN-FANTS	BIRTH WEIGHT 1,000 TO 1,500	1,501 TO 2,000	2,001 TO 2,500	2,501 TO 2,800	NO. OF IN-FANTS	1,000 TO 1,500	1,501 TO 2,000	2,001 TO 2,500	2,501 TO 3,000
Initial weight loss	15	96.2				77	98.0			
Average number of	118		120.4			251		173.8		
grams	393			147.2		290			178.1	
	92				210.7	31				231.8
Birth weight regained	15	8.2..				77	18.6			
Average number of	118		9.4			251		14.4		
days	393			8.0		290			11.8	
	92				8.4	31				12.0
Stay in hospital	15	41.6				77	45.7			
Average number of	118		27.3			251		30.5		
days	393			13.4		290			19.9	
	92				12.5	31				16.8

*All infants under 2000 grams were given breast milk only.

†Includes infants born in homes and other hospitals and brought to Sarah Morris Hospital for subsequent care during years 1930 to and including 1933.

In Table III are shown the mortality rates for the various weight groups during the first twenty-four and forty-eight hours and then for weekly intervals. It should be emphasized in defense of this mortality finding that every premature infant, if only breathing for a few seconds, was recorded as a living birth. It should also be mentioned that of the 134 deaths, 53 died in the birth room and of the 81 infants who reached the nursery, 62 died within the first forty-eight hours.

TABLE III

MORTALITY DURING HOSPITAL RESIDENCE IN A GROUP OF 752 PREMATURE INFANTS

BIRTH WEIGHT IN GM.	NO.	NUMBER OF DEATHS: WITHIN 24 HR.	WITHIN 48 HR.	3-7 DAYS, INCLUSIVE	8-14 DAYS, INCLUSIVE	15 DAYS TO END OF RESIDENCE	TOTAL NUMBER OF DEATHS	MORTALITY PER CENT	INFANTS SURVIVING FIRST 48 HR. MORTALITY PER CENT
Under 1,000	31	29	1	1			31	100.0	100.0
1,001 to 1,500	51	27	2	5	1	1	36	70.6	31.8
1,501 to 2,000	155	27	5	2	2	1	37	23.8	4.1
2,001 to 2,500	418	16	3	5	1		25	6.0	1.5
2,501 to 2,800	97	5					5	5.2	0.0
Total	752	104	11	13	4	2	134	17.8	3.0

Considering the table as a whole, the total mortality of 17.8 per cent is as low as any found in the literature, and if it is permissible to ex-

clude all deaths occurring within the first forty-eight hours, as thought justifiable by Blackfan and Yaglou and also by Hess, the mortality is less than 3 per cent.

Table IV summarizes the data showing the percentage of premature infants who were graduated from the Chicago Lying-In nurseries in the years from 1931 to 1935. It should be mentioned that no premature infants were received from homes or other hospitals.

TABLE IV

PERCENTAGE OF PREMATURE INFANTS GRADUATED

BIRTH WEIGHT IN GM.	NUMBER	GRADUATED		NUMBER SURVIVING FIRST 48 HR.	PER CENT GRADUATED OF INFANTS SURVIVING FIRST 48 HR.
		NUMBER	PER CENT		
1,000 and under	31	0	0	1	0
1,001 to 1,500	51	15	29.4	22	68.2
1,501 to 2,000	155	118	76.1	123	95.9
2,001 to 2,500	418	393	94.0	399	98.5
2,501 to 2,800	97	92	94.8	92	100.0
Totals	752	618	82.2	637	97.0

In Table V are listed the causes of death as revealed by necropsy findings and as judged by clinical signs. Neither upper respiratory infections nor serious digestive disorders played any prominent part in this mortality. A few infants at autopsy showed pneumonic involvement, but this finding was usually associated with atelectasis. The low incidence of infection may be due in part to the fact that not more than four premature infants were together in the same nursery at any one time.

TABLE V

CAUSES OF DEATH OF 134 PREMATURE INFANTS

CAUSE OF DEATH	LENGTH OF LIFE				TOTAL
	UNDER 1 DAY	2-7 DAYS INCLUSIVE	8-14 DAYS INCLUSIVE	15 DAYS TO END OF RESIDENCE	
Congenital weakness	64	11	1	0	76
Accidents of labor	14	9	0	1	24
Pneumonia	0	0	2	0	2
Atelectasis	3	0	0	0	3
Congenital syphilis	0	1	0	0	1
Malformations	9	3	1	1	14
Hemorrhage	0	0	0	0	0
Sepsis	1	0	0	0	1
Asphyxia	13	0	0	0	13
Accidental	0	0	0	0	0
Undetermined	0	0	0	0	0
Total	104	24	4	2	134

The care, hygiene, and nutrition of these 752 premature infants cannot be discussed in detail, but the principles of management will be outlined briefly. The extent to which specialized nursing care is required

depends primarily upon the stage of prematurity. Conservation of heat is the first essential of good care and is accomplished by the use of a heat lamp immediately after delivery. The premature infant may either be covered with a garment of warmed flannel wool or, if the infant is very small, by a light covering of warmed cotton batting and transferred to a Nobel box type of incubator.[4] The regular carrying out of such routine procedures as weighing, bathing and taking of temperature often depends upon the infant's condition.

The most frequent complication occurring during delivery is asphyxia, and the younger the premature infant the more frequent is its incidence. The first step in the treatment of asphyxia is the removal of obstructing material, such as blood and mucus, from the oropharynx or trachea by a tracheal catheter. Pure oxygen or oxygen (95 per cent) and carbon dioxide (5 per cent) should be administered by mask until the color of the infant's skin indicates improvement.

It is often advisable to continue oxygen-carbon dioxide administrations for short periods (3 to 5 minutes) at one-hour intervals for days to forestall cyanotic attacks. The best method of resuscitation, if respiration should cease, is the gentle rhythmical compression of the thorax about 15 times per minute combined with the administration of oxygen and carbon dioxide. It is not always easy to determine the cause of cyanotic attacks frequently seen in premature infants. Often an attack occurs during or after a feeding. Apparently the effort of swallowing and distention of the stomach are contributory causes. Many premature infants suffer from various degrees of atelectasis after birth,[5] and, if this is extensive, it may predispose to cyanotic attacks. Other more serious causes of cyanosis, however, are congenital heart conditions and intracranial hemorrhage.

The handling of a premature infant during any procedure, such as feeding, the taking of the temperature, bathing, weighing, and the changing of the cotton pad or diaper, should be done with as little exposure as possible. Routinely the temperature is taken twice a day, the body is cleansed with olive oil, albolene, or baby oils every other day for two weeks and then every day, and the infant, if very small, is weighed twice a week and later every other day.

The maintenance of body temperature has in all instances been accomplished by the use of a Nobel box type of incubator containing only one heating element, a 40-watt lamp. The very small infants were in addition placed in a service room where the temperature ranged from 80° to 95° F. and where the humidity was high. As a rule, a very small infant is likely to have a somewhat subnormal temperature. If an attempt is made to maintain the premature infant at all times at the supposedly normal level of 98.6° F., decidedly unfavorable results may follow.[1]

Many factors enter into the consideration of feeding and sustaining the nutrition of the smaller premature infant. Proportionally the need of fluids and food is at least equal to that of the full-term infant. However, because of the immature stage of development the premature infant is neither ready nor able to ingest food and fluids in comparable amounts.

All of the 752 premature infants were started on breast milk which was given either by dropper, tube, or bottle. It became necessary in many instances, however, to change the food after a few weeks to a simple artificial formula of two-thirds cow's milk (evaporated or pasteurized) with a 5 per cent dextrin-containing carbohydrate. Feedings were started for most infants about four hours after birth and continued at three-hour intervals eight times during the day. Water was offered by dropper one hour before feeding as long as the milk intake was less than the normal fluid requirement, approximately one-sixth to one-eighth of the body weight. The amount of breast milk given varied with the infant's size. An infant weighing 1,000 gm. may be started on 2 c.c. of breast milk at each feeding; one weighing 1,500 gm., 4 to 8 c.c.; and one weighing 2,000 gm., 16 c.c. After the first few feedings, each alternate feeding may be increased from 1 c.c. to 4 c.c. every day or every other day. It must be emphasized that the amount of food or fluid readily taken will depend even more on the vitality than on the weight.

The very small premature infant can take only limited amounts of food at any one time. To increase the caloric intake but not the volume of the food, a teaspoonful of dryco may be added to every ounce of breast milk, or, if it is desired to increase the minerals and proteins, the formula may include one-third buttermilk or one-third skimmed lactic acid milk. An increase in the protein content of the food is important when the stools are loose or too frequent. In the present routine of feeding very little attention is paid to total calories. The idea that one should strive to give so many calories per pound or per kilogram has been overemphasized. The ideal sought is to feed each premature infant an amount productive of a consistent gain in weight. On such a schedule the birth weight may often be doubled in less than fifty days. A good average gain should be about 30 gm. a day. It is frequently found that premature infants have refractory periods when little or no gain in weight takes place. This growth inactivity or failure to gain weight is not due to an insufficiency of food or lack of care since a stimulant in the form of 10 to 20 c.c. of whole blood injected intramuscularly, preferably in the infant's buttocks, will start the growth impulse. This type of treatment was suggested some years ago by Dr. Blackfan and has been of material value in shortening the duration of the premature infant's residence in the hospital.

Three accessory food factors are given to those premature infants who remain longer than two weeks in the hospital. Iron in the form of ferric

ammonium citrate, 1 drop of a 20 per cent solution, is added to each feeding by the end of the second week. Orange juice and cod liver oil are started in small amounts beginning with the fourth week and the dosage of each increased gradually until one ounce of the former and two teaspoonfuls of the latter are given before the end of the third month.

In the care of these 752 premature infants, the work has been carried on with a continually changing nursing personnel. From the standpoint of the nurse, this frequent rotation has definite advantages, but the vigilance of the staff must necessarily be increased.

SUMMARY

Statistical data and a brief summary of the institutional care of 752 premature infants are presented. The total mortality is 17.8 per cent. Excluding deaths occurring within forty-eight hours after birth, the mortality is less than 3 per cent.

REFERENCES

1. Swanson, Wm. W., Turner, A. R., and Adair, Fred L.: J. PEDIAT 7: 516, 1935.
2. Blackfan, K. D., and Yaglou, C. P.: Am. J. Dis. Child. 46: 1175, 1933.
3. Hess, J. H., Mohr, G. J., and Bartelme, P. F.: The Physical and Mental Growth of Prematurely Born Children, Chicago, 1934, University of Chicago Press, Ch. IV.
4. Parmelee, A. H.: Am. J. Dis. Child. 41: 33, 1931.
5. Farber, Sidney, and Wilson, J. L.: Am. J. Dis. Child. 46: 572, 1933.

MORTALITY AMONG PREMATURELY BORN INFANTS

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THE present high mortality among prematurely born infants constitutes a large part of the general problem of infant mortality in the United States today. At least half the deaths of infants in the first year occur in the first month of life, and of these neonatal deaths nearly half are caused by premature birth.

The infant mortality rate as a whole (infants under one year of age) declined from 1915* until 1933, when the decline gave place to a slight rise, which was followed by another slight rise in 1934. The mortality rate among infants under one month, however, declined much more slowly than that for infants under one year. The mortality rate from premature birth has declined only about half as much as the neonatal mortality rate and only about one-third as much as the infant mortality rate as a whole. The problem of reducing neonatal mortality is, to a great extent, a question of reducing mortality from premature birth.

The extent of the problem of premature birth in the United States can only be estimated. It is probable that there is considerable variation in different communities and different sections of the country and among births in hospitals and in homes. Woodbury[1] found among nearly 23,000 liveborn infants in eight cities that 5 per cent were born prematurely (after a gestation period of eight months or less). In New York State in 1933, 4 per cent of the live births were reported as premature.[2] Schwarz and Kohn[3] found among more than 11,000 infants born at home nearly 3 per cent who were regarded by them as premature because the birth weights were 2,500 gm. or less. On the latter basis recent hospital reports show between 6 and 7 per cent of births to be premature.

When considering how mortality among premature infants may be reduced further, it is desirable to analyze the factors that bring about premature birth, to inquire into the mortality rates and the causes of death among premature infants, to attempt to evaluate the efforts that have been made or are being made to lower this mortality, and to estimate the results achieved. In this paper the discussion of studies that have been made for these purposes will be limited mainly to those made in the United States.

The importance of premature birth as a factor in infant mortality has been referred to frequently over a period of many years in the medical literature of the United States and other countries. Investiga-

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*In 1915 the United States Birth Registration Area was established and since then comparable figures have been available from the Bureau of the Census.

tions on this subject made in the United States are far less numerous and, as a whole, less adequate than those made in other countries. Moreover, since investigators in the United States have, as a rule, used neither a uniform criterion of prematurity nor similar methods of analyzing their figures, comparison of results is not always possible.

Studies of causes of premature birth made so far have shown that in nearly half the cases investigated the causes of the premature birth were not determined. It is apparent, therefore, that further investigations on this subject are needed. Of the known causes of premature birth, that most frequently reported is multiple pregnancy. Other important causes, reported in varying frequency by different authors, are toxemias of pregnancy, syphilis, chronic diseases of the mother such as nephritis and heart disease, and bleeding due to placental abnormalities (placenta previa and premature separation of the placenta).

Although multiple pregnancy is considered the most frequent cause of premature birth, the mortality of infants in this group of cases is probably not very high, since many of them are not so premature as the weight alone would indicate. The toxemias of pregnancy, although apparently not preventable, can probably in many cases be modified in severity by proper prenatal care. In this way the need for induction of labor can often be prevented or delayed until the fetus has reached a viable period. Syphilis, it is hardly necessary to point out, is *the* outstanding preventable cause of premature birth. It is a fact, however, that even in the most enlightened communities syphilis is still reported as a frequent cause. When such conditions as severe cardiac or renal disease exist in a pregnant woman, prolongation of pregnancy may be impractical. Likewise, in certain other conditions, such as bleeding due to placental abnormalities, little can be done with the knowledge at present available to prevent premature birth.

Some causal influences that seem to affect the occurrence of premature births were pointed out in a Children's Bureau study of causes of infant mortality published in 1925.[1] It was shown that a higher proportion of premature births occurred among plural births than among single ones and among male infants than among female. The proportion was high among first infants, infants of young mothers, and infants born at short intervals after preceding births, and it was especially high among infants born to mothers employed away from home during pregnancy. The direct relationship, moreover, that the mother's health bears to prematurity was shown by the very high proportion (39 per cent) of premature births among infants born alive to mothers who died either at confinement or within one month thereafter.

In addition to further studies of the causes of premature birth, studies should be made of methods for prolonging pregnancy safely in the presence of complications, and the knowledge already available should be

more generally applied in an effort to reduce further the incidence of premature birth.

There is great variation in reported mortality among premature infants and some question as to the best methods of caring for them.

A member of the Children's Bureau staff recently visited more than 100 hospitals in twenty-seven large cities of the United States to obtain a general idea of methods commonly used in the care of premature infants and of the results obtained. Although a great variety of methods of care were in use in the different hospitals, in only four had an evaluation of any method been made on the basis of morbidity or mortality. A number of the hospitals, however, later compiled their statistics and reported a mortality varying all the way from 18 to 94 per cent.

Reports published between 1921 and 1934 of studies of the mortality among premature infants, in which any infant having a birth weight of 2,500 gm. or less was classified as premature, show, for studies made in the United States, a mortality ranging from 27 to 77 per cent and, in European countries, from 13 to 55 per cent. Furthermore, recent studies, as yet unpublished, made in four large hospitals in the United States show a mortality between 25 and 34 per cent, averaging somewhat less than that given in the earlier reports.

In evaluating these mortality figures, however, a number of factors must be taken into consideration. All reports available have shown that when studied on the basis of birth weight, mortality is inversely proportional to the weight. For example, in the four hospitals already referred to the mortality for infants weighing less than 1,000 gm. at birth was high, varying between 93 and 100 per cent, whereas for those weighing between 2,000 and 2,500 gm. the mortality was low, varying between 6 and 14 per cent. The mortality for infants in two other intermediate weight groups decreased as the weight range increased. Comparisons of mortality among premature infants should be made only when the weights of the infants included in the groups to be compared fall within certain specified narrow ranges. Moreover, since the mortality for premature infants born at home and brought into hospitals for care is known to be higher as a rule than that for infants born in hospitals and cared for in the hospitals in which they are born, these two groups should be considered separately in evaluating results of care. As has been mentioned, multiple births also should be taken into consideration, as there is some evidence that, when birth weight is the criterion of prematurity, the mortality for premature twins is lower than that for single premature infants.

The extent of the efforts that have been made or are being made to reduce mortality among premature infants is difficult to determine, since, as has been pointed out, reports are not numerous and criteria of prematurity as well as methods of analyzing material have differed in the hands of various investigators; moreover, in reports advocating various

methods of care of premature infants, it is only in rare instances that satisfactory statistical evidence of the results of care has been presented. Although birth weight is probably not the most accurate measure of prematurity, yet for clinical and statistical purposes the adoption of a birth weight of 2,500 gm. or less as the basis for the diagnosis of prematurity would be advantageous since it would set up a uniform standard. Adoption of this standard in the United States would permit comparisons with the results reported by foreign investigators, who have almost without exception used it.

The causes of *death* of premature infants are often difficult to determine, as is shown by the fact that "premature birth" alone is the cause most frequently reported. If pathologic and other laboratory studies were made in these cases, intracranial hemorrhage and septicemia would be found to account for the death of some of them. There is little doubt that premature infants are peculiarly susceptible to intracranial trauma during birth, and intracranial hemorrhage is one of the most important causes of death reported. Infection, particularly general septicemia, although frequently not reported as such because not recognized, is nevertheless another important cause of death. Special studies in which routine cultures of the blood were made of premature infants ill with obscure conditions have shown in a number of instances the presence of blood stream infection in the absence of the usual clinical evidences of it. Atelectasis, a condition that is of course physiologic during intrauterine existence, is also frequently reported as a cause of death, but probably should not be regarded as the primary cause in very immature infants but simply the result of immaturity. The absence of demonstrable pathology in many premature infants who die suggests that they may succumb through lack of certain hormones or other substances which in full-term infants are probably transferred from the mother by the placental route in the last weeks of pregnancy. Some clinical reports[4] tend to confirm these theories, and there is here a field for research, the results of which may offer a greater hope of bringing about reduction of mortality among infants of low birth weight than clinical methods have afforded as yet.

Certain fundamental rules for the care of premature infants have become firmly established through use, such as maintenance of normal body temperature, isolation in an effort to prevent infection, and treatment of asphyxial attacks. Methods of feeding the premature infant are not so well established, since some authorities advocate breast milk as the only food for these infants while others obtain what they consider equally favorable results with artificial feeding. Some advocate frequent feedings of small amounts; others infrequent feedings of somewhat larger amounts; some feed the premature infant only by bottle, medicine dropper, or Breck feeder, others only by gavage, while still others use combinations of these methods. The advocacy of such meth-

ods of treatment as inhalations of carbon dioxide or oxygen or both, parenteral administration of fluids, transfusions of blood, and so forth, varies greatly from clinic to clinic. All these questions will be greatly clarified when more accurate studies of results have been made.

Evaluation by statistical analysis of methods of care of premature infants has been made by a number of workers in this field. Hess,[5] for example, has shown a decrease in mortality over a period of twelve years in the Premature Infant Station of the Sarah Morris Hospital in Chicago. He attributes some of this decrease to the education of physicians and parents, which has resulted in an increase in the number of premature infants sent from the home to the hospital within the first twenty-four hours of birth, and some of it to the use of a special electrically heated "hand ambulance" which protects the infant from chilling during transportation. Blackfan and Yaglou[6] have presented statistical evidence of lowering of morbidity and mortality by the air-conditioning of the nursery so that certain temperature-humidity relationships were maintained. Clifford[7] has pointed out the value of roentgen ray demonstration of fetal development in utero and its practical application in lowering fetal mortality through control of the time at which pregnancy is terminated.

A vigorous city-wide campaign has recently been inaugurated in Chicago by Bundesen[8] to reduce the death rate from prematurity, which he found to be as low as 5 per thousand in some institutions but as high as 500 per thousand in others. The American Pediatric Society in 1934 appointed a committee which is studying the problems of neonatal mortality and morbidity, particularly when due to premature birth. The Children's Bureau, as part of its research program, has undertaken an intensive study of premature infants in an effort to develop methods that may reduce the high mortality now prevailing among these infants.

SUMMARY

Reduction of mortality among prematurely born infants constitutes a large part of the infant mortality problem in the United States today.

Since in a large proportion of cases the causes of premature birth are reported as "unknown," further efforts should be made to determine these causes. Moreover, information now available as to the causes of premature birth should be more generally applied in efforts to prolong pregnancy until the infant is mature enough to survive.

The causes of death of prematurely born infants are in at least half the cases reported as "unknown." Further investigations should be made, since the causes must be understood before attempts to lower mortality can be intelligently made.

The methods of care and treatment of prematurely born infants now in use should be evaluated on the basis of morbidity and mortality studies, and the methods found to be of value should be more widely

applied. Since it is among infants of low birth weight that mortality is highest, further efforts should be made to develop special methods of caring for this group of infants.

It is only when the medical profession and the public become better aware of the problem of the prematurely born infant, and when they make concerted efforts to solve it, that mortality among these infants will be reduced to any great extent.

REFERENCES

1. Woodbury, Robert Morse: Causal Factors in Infant Mortality, Children's Bureau Publication, No. 142, 1925.
2. Personal communication to the author.
3. Schwarz, Herman, and Kohn, Jerome L.: Am. J. Dis. Child. **21**: 296, 1921.
4. Mügel, Gertrud: Monatschr. f. Geburtsh. u. Gynäk. **88**: 79, 1931.
5. Hess, Julius H., Mohr, George J., and Bartelme, Phyllis F.: The Physical and Mental Growth of Prematurely Born Children, Chicago, 1934, The University of Chicago Press, pp. 12-14.
6. Blackfan, Kenneth D., and Yaglou, Constantin P.: Am. J. Dis. Child. **46**: 1175, 1933.
7. Clifford, S. H.: J. A. M. A. **103**: 1117, 1934.
8. Am. J. Pub. Health **25**: 750, 1935.

THE PATHOGENIC SIGNIFICANCE OF "LATE LACTOSE-FERMENTING" COLI-LIKE BACILLI

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SEVERAL years ago one of us[1] reported the not infrequent occurrence of a heterogeneous group of gram-negative, late lactose- or non-lactose-fermenting bacilli, in the stools of infants suffering from summer diarrhea. No definite evidence was obtained that such organisms played an etiologic rôle in this syndrome although in an occasional infant the serum agglutinated the organism isolated from its stool. Since the question of pathogenicity of these organisms is obscure, it was felt justified to review our own experience of the last few years. It was felt that a combined bacteriologic, clinical, and pathologic study of those patients from whom such organisms were recovered might shed some light on this question.

It is difficult, if not impossible, to review the literature concerning this group of organisms with precision because of the lack of differential descriptive detail in many of the reports. Again, the confusing similarity between this group and the paratyphoid group makes a number of the descriptions inadequate.

Some consideration was given to these organisms during the World War in the course of bacteriologic and protozoologic studies of the feces of soldiers convalescing from dysentery and other enteric diseases. Dean, Adamson, Giles, and Williamson[2] studied 488 dysentery convalescents and in 77 instances found organisms that seem to belong to this group. They make no mention whether or not their strains were motile. Douglas[3] reported finding similar organisms in a small group of men who had contracted dysentery in Gallipoli. Fildes,[4] and Dobell, Gettings, Jepps, and Stephens[5] made similar observations on dysentery convalescents. Glynn and Robinson[6] in an intensive study of 2,360 convalescents from enteric disease report, "A non-motile, indol-positive bacillus producing acid and gas in glucose, mannite and maltose was the commonest non-lactose fermenter in the feces of enteritis convalescents and 'normals.' Bacilli like these, but also dulcite fermenters, occurred in 3.2 per cent of 'normals' and in 11 per cent of 'convalescents.'" These authors state further that "indol-positive, paratyphoid-like bacilli are probably very rarely pathogenic; one variety, however, has been found three times in the blood during life; they are often found in the feces of acute and convalescent enteritis cases and sometimes in normal feces."

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Since the World War a few reports have appeared concerning the presence of these organisms in stool cultures. Dudgeon[7] in 1926 reported on their occasional occurrence and thought that they might cause intestinal disorders. Fothergill[1] found them with considerable frequency in the stools of infants suffering from summer diarrhea. He believed that in some instances they may have been of etiologic importance. Johnston and her associates[8] also noted the occasional presence of such organisms in the feces of infants with summer diarrhea. Kriebel[9] isolated twenty-nine strains during the course of a study of the feces of food handlers in the various Harvard dining rooms. These were all healthy individuals.

In 1918 Bronfenbrenner and Davis[10] isolated similar organisms from food during a study of food poisoning. They made the important observation that, by frequent transfer and by increasing the percentage of lactose, these organisms could be adapted to ferment this carbohydrate. For this reason it seemed that the bacilli observed by them were closely related to the colon group.

It would appear from a review of the literature regarding the occurrence of these organisms in the intestinal tract that there is little or no evidence that they are of importance in the production of gastrointestinal symptoms or actual enteric infection. However, more direct evidence has been obtained that they may be pathogenic under special circumstances in the urinary tract. In a study of *B. coli* infections of the urinary tract Dudgeon, Wordley and Bawtree[11] refer to two cases of acute pyelocystitis from which slow lactose-fermenting bacilli were isolated. One of these terminated fatally. Later Dudgeon[12] reported a group of forty-nine cases of infection of the genitourinary tract due to these organisms. He felt that these infections were more severe and lasted longer than ordinary colon bacillus infections. On the other hand, ultimate complete recovery and freedom from organisms was more common. Positive blood cultures were not obtained. Dudgeon and Pulvertaft[13] subsequently reported a more detailed bacteriologic study of these urinary infections.

In Caldwell's study[14] slow lactose-fermenting bacilli were found in 9 per cent of 112 urine specimens. However, the cultural data, as presented, are not sufficient to convince the reader that all these organisms belonged to the particular group under discussion. There was no clear differentiation from members of the dispar group.

A number of investigators, particularly Dudgeon and Pulvertaft,[13] Fothergill,[1] Kennedy, Cummings, and Morrow,[15] and Kriebel,[9] have studied the cultural, biochemical, and serologic characteristics of this group. It will be pertinent briefly to review its outstanding biologic characteristics with special reference to classification.

It should be emphasized that these organisms are easily confused with the paratyphoid group. When fecal material or urine is plated on one

of the differential lactose-containing plates, the nonlactose-fermenting type of colony is produced. Such colonies are essentially no different from those of typhoid, paratyphoid, or dysentery bacilli. When such colonies are picked to Russell's double sugar agar slants, they produce the typical "paratyphoid" reaction, i.e., an alkaline slant with acid and gas production in the butt of the tube. Further study, however, clearly differentiates these organisms from the paratyphoid group. The most striking reaction in this respect is the late fermentation of lactose. This sugar is fermented by the majority of strains after from two to fourteen days' incubation. Practically all of these strains form indol—a valuable differential reaction from the paratyphoid group. Motility is variable although the majority of strains are nonmotile. Most of the strains isolated from the cases described in this study were nonmotile. Further differentiation is obtained by agglutination. Such organisms are practically never agglutinated by the serums of the more common members of the paratyphoid group. If such agglutination does occur, it is only in very low dilution and never approaches the specific titer of such serums. These are the important general characteristics which permit one to separate these organisms from the paratyphoid bacilli.

Our own experience has shown that these bacteria form a very heterogeneous group,[1] both culturally and by cross-agglutination reactions. Kriebel was able to separate her twenty-nine strains into seven subdivisions on the basis of fermentation reactions. It is likely that more variants would have been found if more strains had been studied. Furthermore, we doubt if such grouping would be substantiated by a serologic study.

It is, of course, difficult to place these organisms into any scheme of classification. As a group they possess certain common characteristics which seem to separate them definitely from the well-known gram-negative intestinal bacilli. With respect to their cultural reactions they seem to occupy an intermediate taxonomic position between the paratyphoid and the colon aerogenes groups with, as Kriebel has suggested, a closer resemblance to the colon bacilli. Furthermore, as discussed below, they may be dissociation variants of one of these.

It will be recalled that Bronfenbrenner and Davis found that organisms, probably similar to those under discussion, could be adapted to ferment lactose, a fact which suggested to them close kinship to the colon group. Dudgeon and Pulvertaft were less successful in adapting their "urine" strains to lactose fermentation.

Dulaney[16] in 1928 studied the dissociation of *B. coli communis*. It was found that the S to R change, with distinct difference in the virulence of the variants, could be produced by aging provided that the ultimate reaction of the medium remained alkaline. Dissociation was inhibited by growth in a medium rendered acid by the utilization of

sugars. With respect to the cultural reactions of these variants this author states, "A distinct difference, however, was found in the reactions which the stabilized R form gave on Endo plates and in Russell's double sugar tubes. While the S organism produced the typical acid reaction with characteristic metallic sheen on Endo plates, the R colonies remained colorless. On Russell's double sugar medium the S form soon gave the typical *B. coli* picture while, with the R organism, the slant either remained unchanged or developed very slowly a faint acid reaction." This study suggests that these late lactose-fermenting organisms might have been rough variants of the colon group.

Nungester and Anderson[17] published a contradictory report. They isolated a *B. coli*-like organism from an empyema of the gallbladder and studied its dissociation variants. They produced two forms, a rough variant which fermented lactose and an S variant which did not. The change from the nonlactose-fermenting S form to the lactose-fermenting R form was easily effected, whereas the opposite change was more difficult to produce. Kriebel found that continued growth of her strains in 5 per cent lactose solution resulted in varying degrees of dissociation into lactose-fermenting types. This suggested to her that she was dealing with dissociation variants of the colon group.

Another hypothesis that has been offered to explain the presence of these organisms in the stools of patients with diarrheal disease or in those of convalescents from such disease is that they may be normal inhabitants of the upper intestinal tract and are found in the stools only when the intestine is being rapidly emptied during a diarrheal state due to some other cause. In fact, Dudgeon[7] states, "In my experience slow lactose-fermenters are present in cultures of the feces obtained from the region of the caecum more frequently than from the lower bowel, at the few opportunities which have occurred during life."

In order to test this hypothesis, observations were made at necropsy on 38 patients from various levels of the bowel. The technic employed was as follows: After the intestine was freed from its mesentery, a small transverse cut was made with sterile scissors at the desired level. A sterile cotton swab was inserted through the opening and a small amount of liquid and solid material was obtained. This was emulsified in broth and immediately streaked on eosin methylene blue plates. After incubation, suspicious colonies were picked and carried through to final identification. Cultures were taken in this manner from the midduodenum, midjejunum, upper ileum, lower ileum, cecum, and sigmoid. There was no selection of cases. So far as possible, cultures were taken from consecutive autopsies regardless of the cause of death.

These organisms were recovered from 13 per cent of the cases. There was no significant difference in the frequency with which they were isolated from different levels of the intestinal tract. This would indi-

cate that these organisms do not inhabit one level of the bowel more frequently than another. Furthermore, the gross frequency of positive results in this series was essentially the same as that obtained during the course of routine stool cultures.

During the past few years organisms belonging in this category have been isolated from 107 cases (excluding the above necropsy study). They were most frequently obtained from stool cultures. Occasionally they were isolated from urine and from purulent material such as appendicial abscess. There was no reason to suppose that these organisms were of significance in 94 of these cases. A few of the patients in this group had enteric disease due to known etiologic agents such as the typhoid or dysentery bacillus. In the remaining 13 cases they played a significant part in the production of disease. The individual patients are presented below. Necropsy findings are described for a few cases that present striking features. It is felt that an analysis of these cases may serve to clarify the question of the pathogenicity of the late lactose-fermenting gram-negative bacilli.

CASE 1.—M. C., a six-year-eleven-month-old girl, was admitted because of chronic pyuria. A late lactose-fermenting bacillus was recovered by culture from catheterized urine specimens.

CASE 2.—G. K., a three-year-ten-month-old boy, was brought to the hospital because of diarrhea and abdominal pain for four days and fever and vomiting of one day's duration. He was operated on for a ruptured appendix and localized peritonitis. Cultures of pus from the peritoneal cavity yielded a late lactose-fermenting bacillus, *B. coli*, and *B. pyocyaneus*.

CASE 3.—E. K., a five-year-old boy, was admitted to the hospital for operation for acute appendicitis with abscess formation. A pure culture of a late lactose-fermenting bacillus was obtained from pus from the peritoneal cavity.

CASE 4.—D. P., a one-year-old female infant, had been receiving treatment for congenital syphilis for several months. Intramuscular injections of sulpharsphenamine were being given in the gluteal region. She developed a deep abscess of one buttock, which was incised and drained. A pure culture of a late lactose-fermenting bacillus was cultivated from this pus.

CASE 5.—W. D., a male infant, aged six months, was admitted because of severe pyelonephritis. He was extremely ill for several weeks with a septic, swinging temperature. A late lactose-fermenting bacillus was recovered by blood culture. The same organism was obtained in pure culture from catheter specimens of urine. This patient's serum agglutinated this organism in a dilution of 1:1280.

CASE 6.—J. W., a twenty-month-old infant, was admitted to the hospital because of severe, acute pyelonephritis. A cystogram resulted in a bilateral reflex. The right ureter was tortuous and somewhat dilated. A late lactose-fermenting bacillus was recovered in pure culture from catheterized urine on two occasions.

CASE 7.—P. C., a seven-year-three-month-old girl, was brought to the hospital for operation for a ruptured acute appendix. Pus from the peritoneal cavity yielded a pure culture of a late lactose-fermenting bacillus.

In the above group of cases this organism played an important rôle in the production of disease. It should be pointed out that in these cases the type of local disease produced is identical with that commonly caused by the colon bacillus. In the following cases a description of the pathologic changes is included.

CASE 8.—B. D., a two and one-half-year-old girl was admitted to the hospital because of fever and pain in the left lower abdominal quadrant. Urinary frequency and urgency were additional complaints. Physical examination revealed a large mass in the region of the left kidney. A late lactose-fermenting bacillus was isolated in pure culture from a specimen of urine obtained by catheterization. Diagnosis of perinephritic abscess was made. At operation a large abscess was found surrounding the left kidney and extending down along the course of the left ureter. The kidney was small and largely destroyed. Pus oozed from its cortex. Cultures of the pus yielded *B. coli*, *B. alkaligenes*, and a late lactose-fermenting bacillus. Specimens of bladder urine obtained by catheter during the convalescent period yielded pure cultures of a late lactose-fermenting bacillus. Post-operative convalescence was normal except for continued pyuria.

The patient was readmitted a month after discharge because of continued pyuria. Retrograde pyelograms revealed a distended, sacculated, left ureteral stump. Cultures of bladder urine and fluid from the ureteral stump taken at this time yielded a pure culture of a late lactose-fermenting bacillus. Laparotomy was performed five days later and the ureteral stump removed. Cultures of abdominal fluid and fluid from the ureteral stump taken at operation yielded the same organism. A subsequent culture of bladder urine was still positive. Convalescence from this second operation was uneventful, and the patient has continued in good health.

Pathologic Examination (S-34-106).—The kidney was large. Small, elevated nodules, averaging 0.8 cm. in diameter, were scattered over the external surface. Some of these presented grayish white, necrotic centers with, in one instance, a cratered area. On section the pelvis and calyces occupied about three-quarters of the cut surface of the kidney. Their walls were greatly thickened and their mucosal aspects, grayish red in color. The remaining renal substance measured from 0.2 to 0.3 cm. in thickness. The usual markings were obliterated, and in the subcapsular zones there were about twelve small abscesses, 0.4 cm. in diameter, with dark red hemorrhagic borders. The wall of the ureter was greatly thickened.

Microscopically there was very little well-preserved renal substance. There were extensive necroses and hemorrhages, together with areas of suppuration. Closer to the pelvis, in the remaining cortical and medullary portions, the inflammatory process was of more chronic character with increase in fibrous tissue, tubular atrophy, hyalinization of glomeruli and the presence of many round cells and finely vacuolated monocytes. There was a fibrinopurulent exudate over the pelvic mucosal surface with underlying acute and chronic inflammatory changes, as well as here and there epithelial regeneration. The ureteral mucosa was, for the most part, ulcerated with an underlying thick zone of granulation tissue, extending into and involving the edematous muscular coat. The adventitia was thickened and edematous, with increase in fibrous tissue, perivascular lymphocytic infiltration, occasional thrombosed vessels and a fibrinous deposit on the outer surface in the process of being organized. In sections stained with Gram and Giemsa stains, rare organisms were seen, some of which were gram-negative rods.

The remaining ureteral stump measured 12 cm. in length. It was greatly dilated. The external surface was roughened and reddish gray in color. The ureteral wall was greatly thickened. Microscopically the mucosa was thrown into prominent thickened folds. The overlying, rather thickened, transitional epithelium was intact

with, in the more superficial layers, hydropic cellular changes and occasional intercellular polymorphonuclears. The thickened mucosa was edematous with increase in fibrillar connective tissue, lymphocytic and plasma cell infiltration, and occasional lymphoid nodules. There was increased fibrous tissue throughout the muscular and adventitial coats. Dilated lymphatics, occasionally containing polymorphonuclears, were at times noted in these layers. No organisms were recognized in sections stained by Gram and Giemsa stains.

CASE 9.—Baby F., a six-day-old infant, was brought to the hospital because of twitchings and cyanotic attacks. Delivery was normal, without anesthesia, after a four-hour labor. The infant was cyanotic at birth and was resuscitated with difficulty. Two days before admission he became cyanotic and had frequent generalized convulsions. Physical examination was essentially negative except for slight stiffness of the neck. The clinical impression was that the patient had an intracranial hemorrhage. Lumbar puncture yielded xanthochromic cerebrospinal fluid that was otherwise not abnormal. The patient died six hours after admission.

Necropsy (A-35-16) was performed four and one-half hours postmortem. The body was well developed and nourished, measuring 54 cm. in length. There were no noteworthy external features. The peritoneal, pleural, and pericardial cavities were not remarkable. The umbilical vessels were patent and contained fluid blood.

The *heart* was not remarkable.

The *lungs* anteriorly were light pink, air containing, with a few emphysematous blebs. Posteriorly they were deep red with firm and airless zones. One of these in the posterior portion of the right upper lobe measured 3×2.5 cm. and presented dark red solid cut surfaces, from which bloody fluid could be scraped. A second, in the upper aspect of the right lower lobe, measured 1 cm. in diameter. There were several smaller ones throughout the left upper lobe which measured from 0.3 to 0.4 cm. in diameter, associated with scattered soft, livid atelectatic areas. The bronchi and pulmonary vessels were not remarkable. Microscopically sections from the anterior portions of the lung present a fairly wide bronchioles, alveolar ducts, and infundibula with partially aerated or, less frequently, almost complete atelectatic alveoli. In some of the latter there were cornified epithelial cells, vernix, with occasional hyaline membranes, and rounded alveolar lining cells in part attached, and in part desquamated. Sections from the consolidated areas, on the other hand, revealed hemorrhagic extravasation into the alveoli, polymorphonuclear infiltration of bronchiolar walls with ulceration, and infiltration of the interlobular septums with red blood cells, fibrin, and polymorphonuclears.

The *spleen* weighed 8 gm. (normal weight, 9 gm.). It was soft in consistency. Sectioned surfaces were deep red with poorly defined corpuscular markings. Histologically there were numbers of reticular cells within the follicles presenting, in instances, evidence of phagocytosis. There were many monocytes scattered throughout the pulp with engulfed red blood cells in a number of them.

The *alimentary tract* was not remarkable except that in sections from the colon there were increased numbers of polymorphonuclears in the interglandular stroma, perivascularly in the submucosa, as well as within dilated lymphatics.

The *liver* weighed 144 gm. (normal weight 96 gm.). It was firm, reddish brown and speckled by minute, yellow areas. The cut surfaces were of similar appearance, smooth with somewhat rounded edges. Microscopically the liver cells were large and pale staining with moderate fatty infiltration (scharlach R) in some of the pericentral lobular zones. The sinusoids were moderately dilated with somewhat activated Kupffer cells.

The *kidneys* were not remarkable although in the microscopic sections there were brownish, fairly coarse, pigment granules and fine fatty droplets in Henle's limbs, together with fatty droplets in the epithelial cells of the collecting tubules and urates in some of their lumina.

The *thymus* weighed 2 gm. and histologically presented accidental involutional changes, with depletion of lymphocytes and increase in monocytes, as well as fairly marked, vascular congestion.

The *brain* weighed 435 gm. (normal weight 358 gm.). There was a small amount of subdural blood with a small tear in the right tentorium. The pial vessels over the surface of the brain were markedly congested, and there was some convolutional

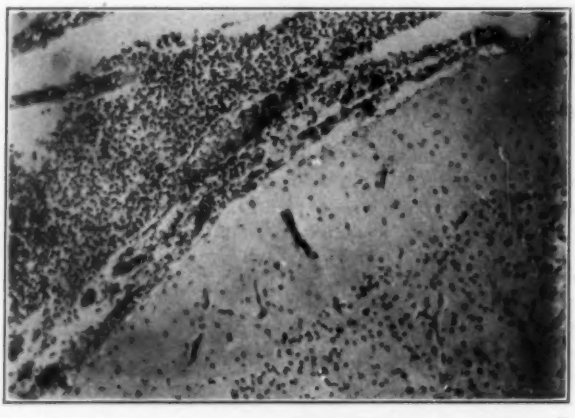

Fig. 1.—(Case 9.) Cerebral cortex with meningeal exudate (× 300). Hematoxylin and eosin.

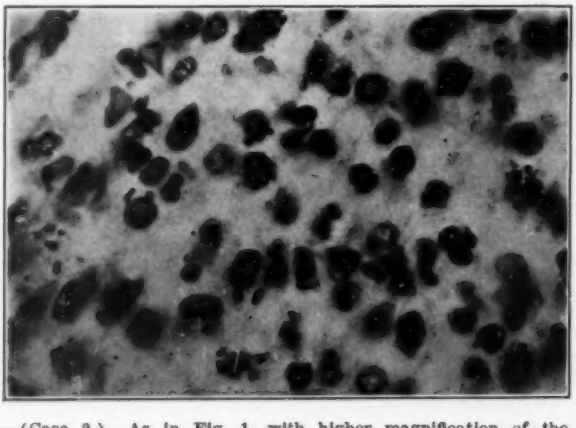

Fig. 2.—(Case 9.) As in Fig. 1, with higher magnification of the meninges. Bacterial rods are seen lying against, but largely within, polymorphonuclears and monocytes (×1175). Giemsa.

flattening. Histologically there was fairly diffuse and moderately marked meningeal infiltration with polymorphonuclears, lymphocytes, and monocytes. Except for edema and congestion, the brain tissue itself was not remarkable.

Both *middle ears* contained thick, yellow, purulent exudate.

The *bone marrow* was markedly congested with small foci of hematopoiesis, chiefly myeloid. There were no foci of necrosis.

In sections stained by Gram and Giemsa stains, one had no difficulty finding bacterial rods (gram-negative) in the blood vessels of the stomach, lung, spleen, adventitial vessels of the aorta, sinusoids of the liver, and in the organizing thrombus of the umbilical vein and in some of the cerebral vessels. Whereas in these the growth probably was in part postmortem, in the meninges there were numerous organisms with many of them within the cells of the exudate, so that there can be no doubt that they were intimately associated with the inflammatory process.

Postmortem bacteriologic cultures yielded a pure growth of a late lactose-fermenting bacillus from the heart's blood. This organism, together with *B. coli* and pneumococci, was recovered from the purulent material in the middle ears.

The *anatomic diagnoses* were acute meningitis, pulmonary atelectasis with acute bronchiolitis and alveolar hemorrhage, subdural hemorrhage (mild) with tentorial tear, and acute otitis media (bilateral), aspiration of amniotic sac contents.

CASE 10.—M. W., a five-day-old female infant, was admitted because of cyanosis and listlessness since birth. Delivery was normal at full term. She was inactive after birth and did not nurse well. Physical examination revealed a flabby, apathetic infant with marked, generalized cyanosis. She presented the facies and other characteristic signs of mongolian idiocy. The skin was dry and scaly. The cardiac dullness was markedly increased to the left, but no murmurs were heard. There was no improvement in the patient's condition. Death occurred on the fourth day after admission. The clinical diagnoses were mongolism and congenital heart disease.

Necropsy (A-31-76) was performed two and one-half hours postmortem. The body measured 46 cm. in length. Postmortem lividity was more marked than usual with generalized, slight, bluish discoloration of the skin of the entire body. The external features were mongoloid. There was flaked, white scaling of the skin over the thorax and abdomen, with a maculopapular rash over the neck and occipital region of the scalp. The papules were deep purplish in color, measured 2 mm. in diameter, and were covered, in some instances, by adherent crusts. The umbilical cord was dry and dark red. The surrounding skin margin was normal.

The peritoneal cavity contained from 25 to 50 c.c. of fibrinopurulent exudate.

The pericardial cavity contained 10 c.c. of similar exudate.

The pleural cavities were clear. The umbilical vein and hypogastric arteries contained fluid and clotted blood without evidence of any inflammatory involvement.

The *heart* weighed 22 gm. (normal weight 19 gm.). In addition to the pericardial exudate, there was an elliptical defect in the membranous interventricular septum, measuring 1.2×0.6 cm. There were no superimposed vegetations. The mitral and tricuspid valves were continuous through the defect with only two leaflets composing the latter. In the apex of the left ventricle there was a firm, dark, red, laminated thrombus, which measured 1.5×0.5 cm., adherent to the walls of the ventricle and septum. Microscopically there was a fibrinopurulent exudate overlying the pericardium. The latter was thickened, increasingly vascular and edematous with scattered polymorphonuclears, lymphocytes, and areas of hemorrhagic extravasation. There were several foci of necrosis and platelet thrombi within blood vessels where the swollen and rounded lining endothelial cells were necrotic. There were dilated lymphatics stuffed with polymorphonuclears. On the endocardial aspect in juxtaposition to the adherent thrombus, there were dilated and, in part, thrombosed intertrabecular recesses with very slight underlying myocardial reaction.

The *lungs* together weighed 50 gm. (normal weight 56 gm.). There were occasional pleural petechiae. Over the posterior portions of the lungs there were scattered, firm, dark red, nodular areas, from the sectioned aspects from which dark red fluid could be expressed. The bronchi were partially occluded by thick,

hemorrhagic, mucopurulent exudate. Microscopically there were wide areas of atelectasis both with markedly congested alveolar septal capillaries, as well as less vascularized septums with pale, clear, lining alveolar cells. In these narrowed atelectatic alveoli there were desquamated pale alveolar cells, polymorphonuclears, some fibrin, rare keratinized epithelial cells, and hyaline membranes. The dark red areas were largely zones of wide hemorrhagic extravasation. The bronchioles were widened and contained in some instances fibrinopurulent exudate. The adventitial coats of the arterial vessels were thickened and edematous. The veins were moderately dilated with occasional mural thrombi. The lymphatics were dilated and contained red blood cells and often fibrinous thrombi.

The *spleen* weighed 7 gm. (normal weight 10 gm.). The pulp was firm and deep red. The corpuscles were scarcely visible. Histologically there were distorted, shrunken, nuclear forms about the periphery of the small follicles, with occasional eosinophiles. Throughout the congested pulp there were a number of large monocytes with either engulfed red blood cells or more often green pigmented spherules or granules. There were rare nucleated red blood cells and occasional blood-forming precursors. In the hilar region there were dilated lymphatics containing fibrin and polymorphonuclears.

The *alimentary tract* was not remarkable except for the esophagus where microscopically there were areas of necrosis and ulceration with underlying acute inflammatory reaction and vascular thrombosis. Similar foci of necrosis and suppuration were noted in the adventitial coat. In the small adjacent lymph nodes, there were widened sinusoids filled with monocytes, polymorphonuclears and red blood cells.

The *liver* weighed 90 gm. (normal weight 123 gm.). It was fairly firm in consistency and of grayish brown appearance. The lobular markings were well defined. Except for one focus of necrosis the sections of liver were not very remarkable microscopically. The Kupffer cells were moderately prominent, with bile pigment and red blood cells in some.

The *kidneys* were not remarkable except for uric acid deposits and moderately dilated calyces and pelves. The ureters were mildly dilated, and in the left one there were constricting points formed by folds of mucosa.

The *brain* was not removed.

The other organs grossly were in no way remarkable. Microscopically there were foci of necrosis with acute inflammatory reaction in peripancreatic, periadrenal, and perirenal tissues with involvement of the interlobular septums of the pancreas as well. The serosal tissues of the fallopian tubes were edematous with widely dilated lymphatics stuffed with purulent exudate. In the leptomeninges of the spinal cord there was a purulent exudate.

Most of the sections were stained by Gram and Giemsa stains with the following findings: Gram-negative rods both intra- and extracellularly within the pericardial necrotic foci and exudate, in the hilar lymphatics of the spleen, in the deeper layers of the esophageal ulcers, in the inflammatory foci of peripancreatic, periadrenal, and perirenal tissues, in the lymphatics of the fallopian tube, and in the exudate within the meninges of the spinal cord. Gram-positive cocci in diploid and chain formation were demonstrable only within the pulmonary exudate and in the surface layers of the esophageal ulcers. There were no demonstrable organisms in the agonal thrombus of the left ventricle.

Postmortem bacteriologic studies revealed a pure growth of a late lactose-fermenting bacillus in the heart's blood and in the pericardial and peritoneal exudate. The same organism, together with pneumococci and *Staphylococcus aureus*, was recovered from the lungs.

The *anatomical diagnoses* were congenital heart disease with interventricular septal defect, mural thrombus of the left ventricle, acute meningitis, acute peri-

carditis, acute peritonitis, bronchopneumonia, acute esophagitis, uric acid renal deposits, and dilatation of the renal pelves and ureters.

CASE 11.—P. L., a seven-day-old male infant, was brought to the hospital because of a rash of four days' duration. The patient was delivered normally at term. No immediate postnatal abnormalities were noted. Four days before admission a "blisterlike" lesion appeared on the chest. Other similar lesions appeared rapidly on the chest and abdomen. Two days before admission the patient

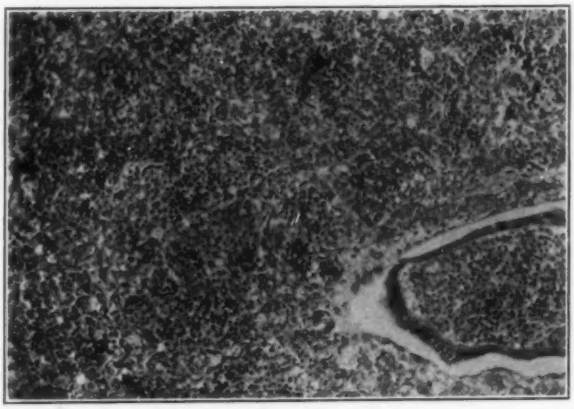

Fig. 3.—(Case 11.) Lung. The alveoli and adjacent bronchioles are filled with cellular exudate (× 300). Hematoxylin and eosin.

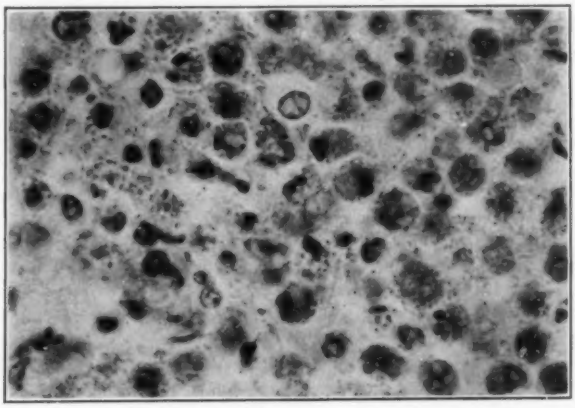

Fig. 4.—(Case 11.) As in Fig. 3. Myriads of bacterial rods within the cells of the alveolar exudate (× 1200). Giemsa.

developed a cough, rapid respirations, and poor color. Physical examination presented an acutely ill, cyanotic infant, breathing with rapid, labored respirations. There were numerous large, bullous lesions over the chest and abdomen. Examination of the lungs revealed evidences of bronchopneumonia. The liver and spleen were palpable. The umbilicus was red and moist. The patient failed rapidly with a gradual increase in cyanosis and respiratory distress. The clinical diagnoses were pemphigus neonatorum and bronchopneumonia.

Necropsy examination (A-33-51) was performed one hour postmortem. The body was well developed and well nourished, measuring 54 cm. in length. The skin was dry with marked desquamation over the lower portion of the abdomen. There were vesicular and bullous lesions, many containing purulent material, over the left cheek, entire left side of the neck, the left arm and wrist, two over the left chest, one medial to the right nipple, and one above the right axilla. The scrotum and buttocks were excoriated and reddened. The sacral spine was bifid for a distance of 2 cm. above the coccyx. The liver and spleen were enlarged and extended three fingerbreadths below the costal margins. The umbilical vessels and heart were not remarkable.

Pleural Cavities.—There were about 6 c.c. of opaque, gelatinous fluid in the left pleural cavity and about 4 c.c. of similar fluid in the right. In addition, the left lung was bound to the parietal chest wall by numerous fine, fibrinous adhesions.

Lungs.—Each weighed 66 gm. (normal weight 24 gm.). The visceral pleural surface of the left lung was slightly roughened with a layer of fibrin over the diaphragmatic aspect. The anterior margins of both lungs were reddish yellow and air containing. Elsewhere, the lungs were reddish purple and firm, particularly the right middle and left lower lobes. The cut surfaces of the latter lobes were dark red, and only a small amount of bloody fluid could be expressed from them. The bronchi contained a moderate amount of reddish, mucoid material, and their mucosal surfaces were slightly thickened and reddened. Microscopically there was an extensive and widespread bronchopneumonic process. The exudate was somewhat variable in character with predominantly large mononuclear cells in varied stages of degeneration, together with polymorphonuclears, occasional red blood cells, serum, and fibrin. The bronchioles were likewise filled with similar exudate with here and there an absence of surface epithelium. Perivascular lymphatics, interlobular septums and pleural tissues and lymphatics were to a variable degree infiltrated or filled with similar exudate. Many of the alveolar septal capillaries were thrombosed and there were mural thrombi in some of the interlobular septal veins. In some of the pneumonic areas there were early necroses containing clusters of bacteria which were clearly gram-negative rods. When stained by Gram and Giemsa stains, myriads of similar organisms, to the complete exclusion of coccal forms, were noted elsewhere, particularly within the large mononuclear cells. Staining with scharlach R revealed many fatty droplets within the cytoplasm of these larger cells. In the less involved portions of lung tissue, there were evidences of aspiration of amniotic fluid with demonstrable keratinized epithelial cells and vernix.

The *spleen* weighed 12 gm. (normal weight 9 gm.). It was soft in consistency and sectioned surfaces were dark red in color. Microscopically the follicles were small with considerable lymphocytic fragmentation. The pulp was congested, but there was no erythrophagocytosis.

The *liver* weighed 230 gm. (normal weight 96 gm.). It was moderately firm in consistency, dark purplish red with fine, yellow mottlings. Cut surfaces were yellowish with intervening translucent, reddish brown parenchyma. Lobular outlines were thereby demarcated. Microscopically there was mild central atrophy with moderate fatty infiltration (scharlach R). The peripheral lobular cells were well preserved. The Kupffer cells were active and, in some instances, brown pigmented.

Lymph Nodes.—Those of the mediastinum were enlarged, reddish purple in color, soft and edematous. Microscopically these presented greatly widened sinusoids, containing numbers of polymorphonuclears, red blood cells and fewer pale, large mononuclear cells. There were occasional small fibrinous thrombi with enmeshed polymorphonuclears. There was apparent depletion of lymphoid elements. The arterial vessels appeared thickened with prominent lining endothelial cells. About some of them there was an increased amount of loose fibrillar connective tissue. The mesenteric nodes were histologically mildly edematous and contained abundant

well-preserved lymphoid tissue. In contrast to the mediastinal nodes, only the medullary sinusoids were widened and contained practically acellular lymph. The peripancreatic nodes presented changes similar to those of the mediastinum but less marked.

The *thymus* weighed 7 gm. Histologically there were marked accidental involutional changes with practically complete replacement of the cortical thymocytes by large, pale mononuclear cells.

Skin.—Histologically the epidermal cells underlying the bullae were swollen and hydropic. Similar swollen cells were not infrequently noted elsewhere in the noninvolved epidermis close to the basal cylindrical cell layer. There were occasional abscesses, either within a hair shaft or within the epidermis involving the orifice of one. The vessels of the papillary layer of the corium were widened and congested. There was a mild degree of edema throughout the corium with scattered lymphocytes and polymorphonuclears. Stained by Gram and Giemsa stains, there were many coccal forms and only infrequent rods within the abscesses.

Postmortem bacteriologic studies showed a pure culture of a late lactose-fermenting bacillus in the heart's blood, the right bronchus, a bulla in the left axilla and in stab cultures from the lungs—right middle and left lower lobes. Cultures of the exudate in the left pleural cavity yielded this organism together with *Staphylococcus aureus*. Both gram-positive cocci and gram-negative rods were seen in smears of the bullous contents.

The *anatomical diagnoses* were pemphigus neonatorum (bullous impetigo), bronchopneumonia, acute pleuritis (bilateral), acute lymphadenitis (mediastinal and peripancreatic), uric acid renal deposits, petechial hemorrhages (mucosa of urinary bladder and adrenal medulla), fatty infiltration of the liver and accidental involution of the thymus.

CASE 12.—J. H., a two-month-old female infant, with an irrelevant family and past history, was admitted because of jaundice and convulsions. Five days before admission the patient became pale and limp. The temperature was 103° F. The following day jaundice was noticed, and the patient had a generalized convulsion lasting three hours. Fever, increasing jaundice, and occasional convulsions continued until admission. On physical examination the patient was found to be moderately jaundiced. The abdomen was distended and presented shifting dullness and a pouting umbilicus. The liver and spleen were enlarged. The patient lived for eight days after admission. The leucocyte count varied between 41,000 and 72,000 cells per cubic millimeter. The urine was loaded with pus cells. On three occasions the blood culture was positive for a late lactose-fermenting bacillus. Death occurred on the eighth hospital day after a series of generalized convulsions.

Necropsy (A-33-70) was performed four and one-half-hours postmortem. The body measured 51 cm. in length and was poorly nourished. There was generalized jaundice. The abdomen was markedly distended. The liver edge was palpable 2.5 cm. and 3 cm. below the costal margin in the right nipple and midsternal lines, respectively. The spleen was palpable 2 cm. below the left costal margin. The peritoneal cavity contained 6 c.c. of clear, amber-colored fluid. The peritoneal surfaces were all smooth and glistening except for filmy adhesions between the anterolateral surface of the spleen and omentum. The kidneys were soft and very large; almost reaching the brim of the pelvis. There were no enlarged mesenteric or periaortic lymph nodes. The lymph glands of the mediastinum were enlarged, soft, and edematous, the largest measuring $0.6 \times 0.4 \times 0.3$ cm. The pleural and pericardial cavities were not remarkable. The umbilical vessels were obliterated. The heart was not remarkable except for mild hypertrophy and the presence of edematous, jaundiced epicardial tissues.

Lungs.—The right weighed 46 gm. (normal weight 32 gm.) and the left 38 gm. (normal weight 30 gm.). Anteriorly the lungs were pale, yellowish pink and air

containing. Posteriorly they were dark purplish red in color, almost airless, with small, dark red, firm areas, the largest measuring 0.7 cm. in diameter. The cut surfaces presented appearances similar to those noted externally, and from the posterior portions a small amount of serosanguineous fluid could be expressed. The pulmonary vessels and bronchi were not remarkable. Microscopically sections from the posterior portions were characterized by a marked degree of lobular pneumonia. The exudate varied in different areas, being composed of serum, densely massed fibrin, polymorphonuclears, red blood cells, and large monocytes. In several instances there were hyaline membranes. The pleural and interlobular septums were edematous and contained dilated lymphatics with acellular lymph. In one instance there was interstitial emphysema. In less involved zones, the bronchioles were frequently filled with exudate, and their parietes were involved in the inflammatory process with extension to, and early ulceration of, the surface epithelium. The alveoli contained many large, pale, vacuolated monocytes and the alveolar septums were approximated and thickened by polymorphonuclear and monocytic infiltration. With Gram and Giemsa stains there were frequent clusters of bacterial rods, some intracellularly, with only rare coccal groups in diploid and chain formation.

The *spleen* weighed 46 gm. (normal weight 13 gm.). It was firm in consistency, with dark reddish purple cut surfaces, presenting rather indistinct, irregular, gray, corpuscular markings. Histologically there was marked increase in numbers of cells in the pulp and sinusoids. These were in part lymphocytes and plasma cells with many immature cell forms and large actively phagocytic monocytes. The latter contained a moderate amount of hemosiderin, fatty droplets (scharlach R), and occasional clustered rods (Gram and Giemsa). There were frequent foci of hematopoiesis. The lining cells of the sinusoids were hypertrophied. In areas of the pulp there were increased numbers of polymorphonuclears.

The *gastrointestinal tract* was not remarkable.

The *liver* weighed 206 gm. (normal weight 136 gm.). It was firm in consistency and of pale brownish yellow color. The cut surfaces were similar in color with distinct markings. Histologically there was fairly marked periportal fatty infiltration (scharlach R) with considerable hemosiderin pigment both within liver cells and in enlarged Kupffer cells. There were occasional foci of necrosis with more frequent single-celled degeneration and necrosis. Frequent hematopoietic foci were noted in the sinusoids and occasionally in portal spaces. The reticular stroma in the periportal zones appeared edematous and increased in amount.

Each *kidney* weighed 53 gm. (normal weight 19 gm.). Externally, when the thin capsule had been stripped, one noted a finely irregular surface, reddish in color with pale yellow mottlings. The cut surfaces were pale, with poor demarcation between cortex and medulla. The calyces and pelves were deeply jaundiced, edematous and thickened (0.1 cm.). Microscopically there was a marked degree of pyelonephritis with purulent exudate within tubules, as well as to a lesser degree in the interstitial tissues. In the latter there were many lymphocytes, monocytes, some plasma cells, many young blood-forming precursors, and some definite foci of hematopoiesis. With Gram and Giemsa stains there were many rods, particularly within the lumen of the tubules, both free and intracellularly, with fewer numbers in the interstitial tissues. The pelvic tissues were thickened, markedly edematous and infiltrated by polymorphonuclears and monocytes. There were occasional hematopoietic foci. There were areas of epithelial metaplasia to that of a more squamous and keratinizing type.

The *ureters* and *bladder* were not remarkable.

Of the other organs there were, histologically, several small foci of necrosis in the adult cortex of the adrenal with involution in great part of the fetal cortex. In the medulla there were collections of cells of leucopoietic type and in the periadrenal fetal fat, perivascular foci of hematopoiesis. There was from mild to

marked accidental involution of the thymus, with loss of the usual corticomedullary distinctness associated with depletion of lymphocytes, variable degrees of fibrosis, and infiltration with large pale vacuolated monocytes. A section of one lymph node revealed moderate lymphoid hyperplasia, some sinus endothelial proliferation and infrequent foci of leucopoietic cells. The bone marrow was chiefly leucopoietic. A small focus of polymorphonuclear infiltration was noted in a section of gasserian ganglion adjoining the dural aspect. The brain, spinal cord, thyroid, trachea, parathyroids and aorta were grossly and microscopically in no way unusual. Both middle ears contained serohemorrhagic exudate. The tympanic membranes were intact but slightly reddened. The mucosa of the mastoid antrums was moderately reddened.

Bacteriologic Examination.—A late lactose-fermenting bacillus was isolated from the heart's blood, left bronchus, ureter, left middle ear, ileum, and jejunum.

Anatomical Diagnoses.—Acute bronchopneumonia; pyelonephritis (bilateral, acute otitis media; hyperplastic splenitis; fatty infiltration of the liver with focal necroses; hematopoiesis, liver, spleen, kidney, adrenal; accidental involution of thymus; jaundice.

CASE 13.—B. C., a ten-week-old female, was admitted because of drowsiness, fever, and diarrhea of three days' duration. Physical examination revealed an acutely ill, listless, slightly cyanotic infant with no definite localizing signs of pathology. Following admission the patient continued to have diarrhea and ran a high, sustained fever. The urine was loaded with white cells. The course was progressively downhill and death occurred three days after admission.

Necropsy (A-32-31) was performed two and one-half hours postmortem. The body was fairly well developed but poorly nourished and measured 51 cm. in length. The serous cavities, unbilical vessels, and heart were not remarkable.

Lungs.—The right lung weighed 68 gm. (normal weight 35 gm.), and the left, 52 gm. (normal weight 30 gm.). The posterior portion of all lobes, particularly the lower, were firm, nodular and dark, purplish red in color. On section these areas were deep red, and from them thick, dark red fluid could be expressed. The anterior portions of the lungs were pink and air containing. The bronchi contained a small amount of blood-tinged, mucoid exudate. Histologically there was a diffuse exudative process, chiefly of seropurulent or fibrinopurulent character. There were also many large phagocytic mononuclear cells. The bronchioles contained a small amount of purulent exudate and some cellular débris. The interlobular septums were thickened, edematous and infiltrated largely with mononuclear cells. They contained dilated lymphatics filled with serous exudate. Some of the larger blood vessels were thrombosed. There were numerous gram-negative rods in the alveolar exudate, many within the large monocytes and some, apparently, in the alveolar septums (Gram and Giemsa stains). Only rare coccal clusters were seen.

The *spleen* was not enlarged. It was fairly firm in consistency. The pulp was dark red in color. Microscopically there were many large phagocytic cells in the pulp and sinusoids with moderate deposits of hemosiderin.

The *alimentary tract* was not remarkable except for the distal portion of the ileum where there were numerous grayish red Peyer's patches with occasional small, irregular, shallow ulcers from 1 to 2 mm. in diameter. The bases of these were flat and pale gray. The surrounding margins were not reddened. Histologically these ulcers extended to, or were deep to, the muscularis mucosae. The underlying reaction was proliferative in type, with fibrosis and perivascular and diffuse lymphocytic and monocytic infiltration. There was very little superficial exudate. An occasional thrombosed venule was encountered close to the ulcerated surface. In the submucosa, muscularis and serosa there were dilated lymphatics, containing lymphocytes and large pale degenerating monocytes. The serosa was thickened and edematous, increasingly vascular, with scattered monocytes and increased num-

bers of fibroblasts. The uninvolved portions of ileum presented a curious rounding of the blunted villar and interglandular surfaces. Both villi and interglandular tissues were quite cellular, more so in some areas than in others, but without acute inflammatory changes. Numerous gram-negative rods covered the surface of the ulcers but none could be recognized deeply (Gram and Giemsa stains).

The *liver* and *pancreas* were not remarkable.

Kidneys.—The right weighed 24 gm. (normal weight 20 gm.) and the left, 20 gm. (normal weight 19 gm.). Except for the lower pole of the left kidney, the perirenal tissues, capsule, and renal substance itself were not remarkable. In the former region there was scarcely any demarcation between cortex and medulla, the sectioned aspect appearing pale gray and edematous. The pelves were slightly dilated but free of exudate. Sections from the lower pole of the left kidney revealed extensive parenchymatous destruction, largely cortical, with several small abscesses and diffuse and heavy lymphocytic, monocytic, and polymorphonuclear infiltration. The tubules, in less involved areas, were compressed with epithelial

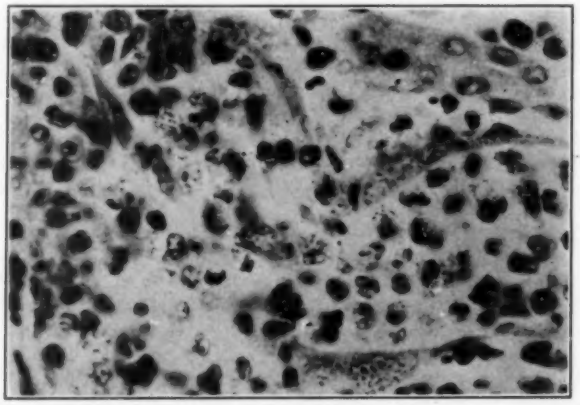

Fig. 5.—(Case 13.) Kidney. Bacterial rods within greatly enlarged and expanded tubular epithelial cells, also in the cells of the exudate interstitially and within the tubular lumen (×1225). Giemsa.

degenerative and regenerative changes and were filled with exudate similar to that in the interstitial tissues. Numerous gram-negative rods could be demonstrated both free in the lumen and interstitial tissues as well as intracellularly within monocytes and polymorphonuclears. In some instances the epithelial cells contained large numbers of these organisms and were thereby enlarged and expanded (Gram and Giemsa stains). The peripelvic tissues were edematous and very lightly infiltrated with lymphocytes and polymorphonuclears. The pelvic tissues were likewise mildly involved. The ureters and bladder were not remarkable.

The *costochondral rib junctions* were convex toward the metaphysis with general broadening in the ephiphyseal region. Microscopically there was irregular proliferation of cartilage with irregular penetration by rather poorly vascularized, but highly cellular and fibrillar marrow. The fibrous marrow extended for a short distance within the diaphysis and in it there were longitudinal and transverse trabeculae with fair osteoid deposition and some remaining central cartilage. Higher up in the shaft there was a series of transverse bars, not too well calcified. The periosteum was not remarkable. The chondral nutrient vessels were surrounded by an increased amount of cellular fibrillar connective tissue. The

marrow was quite cellular and predominantly granulocytic. There were small foci of early necrosis. In the vertebral sections there was moderate histiocytic phagocytosis.

The *thymus* weighed 5 gm. and histologically presented accidental involution with large numbers of pale monocytes, actively phagocytic, and many eosinophilic myelocytes. One of the enlarged edematous nodes associated with the capsule of the thymus presented mild acute inflammatory changes. The peripheral sinus was dilated, containing polymorphonuclears and deposits of fibrin with, infrequently, the presence of a gram-negative rod (Gram and Giemsa stains). Elsewhere the node was edematous and congested, diffusely and lightly infiltrated with polymorphonuclears with increased numbers of littoral cells and monocytes.

Except for a mild inflammatory reaction in the epidural tissues of one section of spinal cord, the central nervous system was not remarkable.

Both middle ears contained a thin serous exudate.

Bacteriologic studies revealed a late lactose-fermenting bacillus in the heart's blood, right middle ear, left middle ear, ileum, and colon.

The *anatomical diagnoses* were chronic ulcerative enteritis, acute bronchopneumonia, pyelonephritis, acute lymphadenitis (mediastinal), rickets, accidental involution of the thymus, otitis media (bilateral).

DISCUSSION

It is of interest to note the variety of lesions caused by this organism as well as their character in the different age periods. In the youngest (Case 9) there was an overwhelming bacteremia with little localization. The organisms were found in the small blood vessels of many viscera, often accompanied by vascular congestion and in the lungs by alveolar hemorrhage. There was a frank meningitis, and the organisms could be demonstrated readily within the cells of the exudate.

In Case 10 there was again widespread bacterial dissemination, but here it was associated with many foci of inflammation, chiefly, however, in serous cavities, peritoneum and pericardium, as well as in the meninges.

In Case 11 the organisms were chiefly localized in the lungs where they were unquestionably the causal agent in the extensive and marked pneumonic process. Countless numbers of them were present largely within the cells of the exudate. The acute pleuritis and mediastinal lymphadenitis were accompaniments of the pneumonia. The bullous impetigo was probably incidental.

The above three infants were under ten days of age.

Case 12 (patient aged two months) presented evidences of a fairly long-standing septic process indicated by the poor nutritional state, the arrest of growth, the persistent extramedullary hematopoiesis and the enlarged, cellular spleen. The oldest lesion, in point of reaction, was the pyelonephritis. The pneumonia and otitis media were quite recent.

This apparent fact that the organisms might lodge in certain organs and give rise to a continued inflammatory process with subsequent wider dissemination is again borne out in Case 13 (patient aged two and one-half months). The ulcers of the ileum are clearly of long-standing dura-

tion, with the pyelonephritis of about the same or slightly shorter duration. Again in this case, as in the former, the pneumonia and otitis media were more terminal in character and were associated with a generalized septicemia.

In the older aged group of living patients these organisms were important causal agents of pyelonephritis in three, peritonitis associated with appendicitis in three, and an abscess of the buttocks in one.

In taking the 13 cases as a group, therefore, the incidence of specific lesions was as follows: 6 with pyelonephritis, 4 with peritonitis, 4 with pneumonia, 3 with otitis media, 2 with meningitis, and one each with pericarditis and pleuritis.

In these cases in early infancy, as Dr. Wolbach has frequently stressed, there is a striking resemblance to a disease in newborn calves, fully described in a series of papers by Theobald Smith and his associates.[18-21] Calves, deprived of colostrum, frequently develop diarrhea (scours), exudative arthritis, insterstitial nephritis, pneumonia, and omphalitis. Scours is caused by *B. coli*. It is associated primarily with the overgrowth of the organism in the lower small intestine with continued spread toward the duodenum, so that in advanced cases the mucosa may be carpeted by layers of colon bacilli extending from the duodenum to the ileocecal valve. Concomitant with this, in the earliest stages, there is wide dissemination so that the organisms can be cultured readily from the spleen, lungs, and kidneys. Histologically they are present in large numbers within dilated small blood vessels which, at times, may be thrombosed and accompanied by smaller or larger areas of hemorrhagic extravasation. In the later stages of the disease there is a frank inflammatory reaction with localization chiefly in the kidneys, joints, and lungs. In almost no instance is there intestinal ulceration. Although the mortality amongst calves with scours is high, some recover, and the lesions probably heal. The gray, patchy, renal lesions, the so-called *weisse Fleckniere* or *nephritis maculosa alba* in older animals are considered to be such healing or healed forms of nephritis.

This anatomic analogy between scours in calves and widespread colon bacillus infections in infants does not hold when the two species are compared immunologically. There is no striking evidence that the human infant derives maternal antibodies through the colostrum. In man the transfer of antibodies to the fetus occurs through the placenta by virtue of its greater permeability for such substances as compared to the bovine placenta.

In this group of cases it seems logical to assume that these late lactose-fermenting bacilli behaved like the colon bacillus, by virtue of their widespread distribution, multiple foci of suppuration, and predilection for the kidney. The pathologic findings in a series of cases of colon bacillus septicemia in newborn infants have been compared with the findings in these cases. They are essentially similar. It is well known

that the colon bacillus produces lesions similar to those described here in the older age group.

As a result of this study, therefore, it is felt that this group of late lactose-fermenting bacilli is in no way different, in its pathogenic significance, from the colon bacillus. Under ordinary circumstances these organisms are normal inhabitants of the intestinal tract in a small percentage of individuals. When they are associated with the production of disease, it is under circumstances identical with those which might be associated with the colon bacillus.

While the problem of the exact biologic classification of this group is not settled, our study lends support to the opinion that they are either closely related to, or are variants of, the colon bacillus.

It should be reiterated that, from the point of view of bacteriologic diagnosis, these organisms are easily confused with the paratyphoid group. Elsewhere in this paper the differential characteristics have been discussed.

SUMMARY

The literature is reviewed concerning a group of late lactose-fermenting bacilli.

The biologic characteristics of these organisms are described and discussed.

A series of cases is described in which these organisms were of pathogenic significance. It is pointed out that in some cases they may invade widely and cause a variety of lesions entirely analogous to those occasionally caused by the colon bacillus.

REFERENCES

1. Fothergill, L. D.: J. Infect. Dis. 45: 393, 1929.
2. Dean, H. R., Adamson, R. S., Giles, J. D., and Williamson, R.: J. Roy. Army M. Corps 28: 428, 1917.
3. Douglas, S. R.: Medical Research Committee, Special Report Series, No. 6, 1917.
4. Fildes, P.: Medical Research Committee, Special Report Series, No. 6, 1917.
5. Dobell, C., Gettings, H. S., Jepps, M. W., and Stephens, J. B.: Medical Research Committee, Special Report Series, No. 15, 1918.
6. Glynn, E., and Robinson, A. L.: Medical Research Committee, Special Report Series, No. 7, 1918.
7. Dudgeon, L. S.: J. Hygiene 25: 119, 1926.
8. Johnston, M. M., Brown, A., Tisdall, F. F., and Fraser, D. T.: Am. J. Dis. Child. 45: 1, 1933.
9. Kriebel, R. M.: J. Bact. 27: 357, 1934.
10. Bronfenbrenner, J., and Davis, C. R.: J. M. Research 39: 33, 1918.
11. Dudgeon, L. S., Wordley, E., and Bawtree, F.: J. Hygiene 20: 137, 1921.
12. Dudgeon, L. S.: J. Hygiene 22: 348, 1924.
13. Dudgeon, L. S., and Pulvertaft, R. J. V.: J. Hygiene 26: 285, 1927.
14. Caldwell, J. A.: J. Infect. Dis. 43: 353, 1928.
15. Kennedy, J. A., Cummings, P. L., and Morrow, U. M.: J. Infect. Dis. 50: 333, 1932.
16. Dulaney, A. D.: J. Infect. Dis. 42: 574, 1928.
17. Nungester, W. J., and Anderson, S. A.: J. Infect. Dis. 49: 455, 1931.
18. Smith, Theobald, and Little, R. B.: J. Exper. Med. 36: 181, 1922.
19. Smith, Theobald, and Little, R. B.: J. Exper. Med. 36: 453, 1922.
20. Smith, Theobald, and Orcutt, M. L.: J. Exper. Med. 41: 89, 1925.
21. Smith, Theobald: J. Exper. Med. 41: 413, 1925.

THE TREATMENT OF PERTUSSIS WITH AN INTRANASAL ANTIGEN

Preliminary Report

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DURING the interval between May, 1935, and February, 1936, we treated twenty-four active cases of whooping cough in various stages of the disease by the intranasal administration of a soluble antigen prepared from the *Hemophilus pertussis*. The antigen consisted of a solution of soluble substances derived from recently isolated cultures of *Hemophilus pertussis* and represented the soluble protein of about 20,000 million organisms per cubic centimeter.

Method of Administration.—The patient was placed in the recumbent posture with the head held in a dependent position below the level of the body. Ten drops of the antigen were instilled in each nostril. The patient was kept in this position for two or three minutes in order to permit proper absorption. Treatments were usually given daily; in some cases they were given every second day. The total number of treatments varied from four to twelve.

ANALYSIS OF CASES

In addition to the twenty-four patients with whooping cough, 3 contact cases were treated prophylactically. Ten control cases were followed simultaneously, most of these being in the same families as the treated children. This gave us an opportunity to compare the severity of the untreated cases with those which were treated. Although the treatment was first instituted in May, 1935, most of the cases were treated during the interval of November to February when whooping cough is usually at its worst. The youngest patient was seven months old; the oldest was eleven years old.

Results.—The results were graded according to the degree of improvement. The following code is used in Table I in order to tabulate the degree of improvement.

"A"—Marked improvement. Definite decrease in the number and severity of paroxysms. Definite decrease in the duration of the illness. The average duration of the illness in this group was 15.1 days after the first treatment. The average duration of the illness from the date of onset was 25.7 days.

"B"—Moderate improvement. In this group there was a decrease in the number and severity of paroxysms, but there was no great de-

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crease in the duration of the illness. The average duration after the first treatment was 20.7 days, and the average duration from the date of onset was 32.4 days.

"C"—Slight or no improvement. In this group there was either no improvement whatsoever or a questionable degree of improvement. In a few instances the treatment was begun late, and the improvement observed after several treatments may have been the result of a spontaneous improvement which often occurs during the fourth week of the illness. The average duration after the first treatment in this group was 23.5 days, and the average total duration from the date of onset was 34.7 days.

Using the above code the results in general, regardless of the type of case treated or the time at which treatment was begun, were as follows:

A—(Marked improvement)—11 cases.....45.8 per cent
B—(Moderate improvement)—7 cases.....29.2 per cent
C—(Slight or no improvement)—6 cases.....25.0 per cent

It will thus be seen that definite improvement occurred in 75 per cent of the cases. It was possible to shorten the total duration of the disease to a minimum of 17 days and an average of 25 to 35 days depending upon the promptness of the treatment.

An analysis of Table I will show that results were more favorable when treatment was begun early. Results were particularly good in those cases in which treatment was started during the first 10 days. Eleven cases were treated within 10 days after the onset of the cough. The results showed 7 in Group A, 3 in Group B, and only 1 in Group C. Eight cases were treated between 11 and 19 days after the onset. Of these cases 4 were in Group A, 2 in B, and 2 in C. Out of a total of 5 cases treated after 20 days, only 1 fell in Group A; 1 was in Group B; and 3 were in Group C. This demonstrates clearly that treatment must be instituted early to obtain favorable results.

In some cases the results were quite striking. Cases 7 and 8 showed especially good results. Both of these patients had severe attacks before treatment was begun. Other members of the family in each case were used as untreated controls. In Case 7 the whoop completely disappeared after four treatments and in Case 8 after five treatments. They both continued to cough occasionally during the next 9 or 10 days. The control cases in both families had severe attacks and continued to have paroxysmal seizures of coughing for a total of six to eight weeks as compared with four weeks in the treated cases (the last 10 days of which the patients had only a mild cough). In several of the cases classed under Group A, the whoop and vomiting disappeared 6 or 7 days after treatment was begun. However, they continued to have a mild cough for some time afterward.

TABLE I

ACTIVE CASES TREATED WITH INTRANASAL ANTIGEN

CASE	AGE	DURATION OF ILLNESS BEFORE TREATMENT (DAYS)	NUMBER OF TREATMENTS	TYPE OF ATTACK BEFORE TREATMENT	RESULT			REMARKS
					DURATION OF COUGH AFTER FIRST TREATMENT (DAYS)	TOTAL DURATION OF COUGH (DAYS)	DEGREE OF IMPROVEMENT	
1. G. W.	3 yr.	7	5	Mild	10 Mild attack	17	A	Exposed to brother.
2. T. W.	1 yr.	6	5	Mild	14 Mild attack	20	A	Three other children in family were not treated. They had severe attacks lasting 6 to 8 weeks.
3. M. D.	3 yr.	14	5	Moderate	14	28	A	Marked improvement noted after 7 days.
4. P. D.	7 mo.	5	5	Mild	14	19	A	Marked improvement after 4 treatments.
5. M. P.	5 yr.	13	5	Severe	16	29	A	Improvement noted at end of 5 treatments.
6. A. Z.	5 yr.	10	9 (over 15-day period)	Severe	21	31	A	Severe case. Marked decrease in number and severity of paroxysms after 6 treatments.
7. M. O.	3 yr.	15	5	Severe	14	29	A	Whoop disappeared after 4 treatments.
8. L. H.	5 yr.	14	5	Severe	14	28	A	Whoop disappeared after 5 treatments. Two other untreated members of family were severe cases.
9. N. T.	7½ mo.	21	5	Severe	14	35	A	Marked improvement after 5 treatments.
10. D. B.	11 yr.	5	5	Mild very early	15	20	A	Very early case. Contact with sister.
11. P. P.	3 yr.	7	9 (over 12-day period)	Mild	20	27	A	Paroxysms were mild and infrequent. No vomiting.
12. R. B.	6 yr.	8	10 (over 14-day period)	Moderate	22	30	B	Paroxysms fewer in number and severity.

TABLE I—CONT'D

CASE	AGE	DURATION OF ILLNESS BEFORE TREATMENT (DAYS)	NUMBER OF TREATMENTS	TYPE OF ATTACK BEFORE TREATMENT	RESULT			REMARKS
					DURATION OF COUGH AFTER FIRST TREATMENT (DAYS)	TOTAL DURATION OF COUGH (DAYS)	DEGREE OF IMPROVEMENT	
13. B. H.	6 yr.	13	6	Severe	23	36	B	Paroxysms fewer in number and less severe.
14. S. W.	6 yr.	10	5	Severe	21	31	B	Moderate improvement. Attack shorter than usual but paroxysms severe.
15. R. H.	3 yr.	8	6	Severe	25	33	B	Moderate improvement.
16. J. S.	6 yr.	23	5	Severe	12	35	B	Treatment late.
17. R. H.	13 mo.	6	6	Severe	24	30	B	
18. M. D.	3 yr.	14	9	Severe	18	32	B	Improvement noted after 7 treatments.
19. B. B.	3 yr.	14	4	Severe	28	42	C	Very little improvement.
20. E. T.	15 mo.	24	4	Severe	21	45	C	Late case. No improvement.
21. W. W.	6 yr.	20	5	Severe	15	35	C	Slight improvement.
22. M. A.	2 yr.	19	12	Severe	28	40	C	Some improvement after 10 days. Had occasional paroxysms for 4 weeks.
23. E. O.	5 yr.	28	5	Severe, late	21	49	C	Some improvement at end of 1 week, but treatment was late, and this may have been spontaneous.
24. G. Z.	7 mo.	9	12 (over 16-day period)	Severe	28	37	C	Some decrease in number and severity of paroxysms but cough continued for 4 weeks.

TABLE II

RELATIONSHIP OF RESULTS TO THE TIME AT WHICH TREATMENT WAS STARTED

I. Cases treated within 10 days from onset of cough				11
Marked improvement	(A)	7	63.6%	
Moderate improvement	(B)	3	27.3%	
Slight or no improvement	(C)	1	9.1%	
II. Cases treated between 11 and 19 days from onset				8
Marked improvement	(A)	4	50%	
Moderate improvement	(B)	2	25%	
Slight or no improvement	(C)	2	25%	
III. Late cases (treated 20 or more days from onset)				5
Marked improvement	(A)	1	20%	
Moderate improvement	(B)	1	20%	
Slight or no improvement	(C)	3	60%	

In all of the cases the parents were requested to keep an accurate record of the number of paroxysms per day together with a description of the severity of the paroxysms and the number of attacks of vomiting which occurred. In most cases in Group A or B the paroxysms would diminish in number from fifteen to twenty per day to five or six per day after a few treatments. The number of attacks of vomiting would decrease. In most cases the paroxysms were milder. but in some they continued to be severe even though the number had decreased to five per day. In general, the parents stated that they felt that these children had milder attacks of whooping cough than neighbors' children who were untreated or than others of the family who were untreated.

Prophylaxis.—We are not in a position to make any definite statements about the value of this method of treatment as a prophylactic measure. Three contact cases were treated before any cough developed. All of these patients had intimate contact with other members of the family and were all over one year of age. Two developed a mild form of pertussis characterized by a short paroxysmal cough but not associated with any whoop or vomiting. The cough lasted from two to three weeks. The third patient did not develop any symptoms. It would, therefore, seem that this method of treatment may be of value in the prophylactic treatment of contact cases.

Controls.—Ten patients were used as untreated controls. Most of these children were in families in which other members were being treated. The average duration of the cough in this group was fifty days. The paroxysms were more frequent and more severe than those of the treated cases.

COMMENT

Vaccine therapy has been used in the treatment of whooping cough during the past twenty-five years. The type of vaccine, the method of administration, and the results have varied considerably. There has been considerable doubt about the rôle of the Bordet-Gengou bacillus in the etiology of pertussis. However, work during the past three

years has corroborated the view that this bacillus is the direct cause of the disease. Madsen[1] employed a vaccine in the prophylaxis of the disease and reported good results. He used forty-eight-hour blood agar cultures—in a strength of 10,000 million bacilli per cubic centimeter. Three injections of 0.5, 0.7, and 1.0 c.c., respectively, were given at intervals of three to four days. He was able to prevent the disease in 458 out of 1,832 vaccinated children in the Faroe Islands; only 8 patients out of a total of 446 unvaccinated cases did not become infected. Sauer[2, 3] used a freshly prepared vaccine—with a strength of 10,000 million per cubic centimeter—giving a total of 7 to 8 c.c. in three weekly injections. He reported 169 definitely exposed patients over a period of seven years, none of whom developed typical whooping cough.

MacDonald and MacDonald[4] made some interesting observations on the etiology and prophylaxis of the disease. Four brothers were used in the experiment. Two brothers were vaccinated against whooping cough according to the method of Sauer; the other two were not vaccinated. Five months later the four boys were inoculated intranasally with a filtrate from a freshly prepared culture of *Hemophilus pertussis*. The two vaccinated boys remained free from symptoms; their cough plates were normal and their blood counts remained normal. The two who were not inoculated developed typical attacks of whooping cough.

All of these observations seem to establish definitely the *Hemophilus pertussis* as the cause of whooping cough and the value of large doses of vaccine for its prophylaxis. However, the value of vaccine in the active treatment of definitely established cases has been of questionable value. Sauer does not advise the use of his vaccine for treatment and states that three months are required for immunity to develop.

Any treatment which may shorten the course of whooping cough or alleviate the symptoms is certainly valuable. In 1933, Krueger, Nichols, and Frawley[5] described a method for preparation of a new pertussis antigen. Frawley, Stallings, and Nichols[6] used this antigen in the treatment of 165 active cases after the onset of symptoms. They reported good results in 69 per cent of the early cases and 45 per cent of the later cases. They used daily hypodermic injections of 0.1 c.c. increasing until 1.0 c.c. was given. Frawley[7] later recommended the use of much larger doses, using 5 c.c. twice daily, the total amount given varying from 25 to 122 c.c.

Zoeller and Ramon[8] in 1927 described an intranasal method of administering diphtheria toxoid with remarkable success. Friedman, Esserman, and Black[9] in 1934 described a method of immunizing children against scarlet fever by the intranasal instillation of scarlet fever toxin. They used this method in two groups of cases and reported

complete immunity in 60 per cent and 71 per cent of these groups and partial immunity in many others.

An intranasal method of administering a pertussis antigen appealed to us for three reasons: (1) The treatment avoids the necessity of the use of the hypodermic needle to which the children and parents usually object. (2) It can be administered very easily by the mother. (3) There is complete freedom from reactions.

The antigen which we used was prepared by the laboratories of the Sharp & Dohme Company according to the following method:

The cultures of *Hemophilus pertussis* were grown on blood agar. They were then macerated in physiologic saline adjusted to pH 8.4. The insoluble residue was discarded, and the soluble protein was precipitated with acetone. The acetone precipitate, after removal of the acetone, was dissolved in physiologic salt solution to which a mercurial preservative had been added. The final product represented the soluble protein of about 20,000 million organisms per cubic centimeter.

We realize that the number of cases in this series is small. However, we feel that the high percentage of favorable results and the simplicity of the method of treatment definitely class this intranasal antigen as a valuable therapeutic procedure in the treatment of active cases of whooping cough.

SUMMARY

1. Twenty-four active cases of whooping cough were treated with an intranasal antigen.

2. Of this series 45.8 per cent showed marked improvement; 29.2 per cent showed moderate improvement; 25 per cent showed slight or no improvement.

3. The antigen was given daily or every second day for from four to twelve treatments.

4. It was used prophylactically in three cases: two patients developed mild attacks and one patient did not develop any symptoms.

5. The antigen can be administered with ease. There are no reactions, and the nasal mucosa is not irritated.

REFERENCES

1. Madsen, Thorvald: J. A. M. A. **101**: 187, 1933.
2. Sauer, Louis: J. A. M. A. **100**: 239, 1933.
3. Sauer, Louis: Am. J. Pub. Health **25**: 1226, 1935.
4. MacDonald, H., and MacDonald, E. J.: J. Infect. Dis. **53**: 328, 1933.
5. Krueger, A. P., Nichols, V. C., and Frawley, J. M.: Proc. Soc. Exper. Biol. & Med. **30**: 1097, 1933.
6. Frawley, J. M., Stallings, M., and Nichols, V. C.: J. PEDIAT. **4**: 179, 1934.
7. Frawley, J. M.: J. PEDIAT. **7**: 692, 1935.
8. Zoeller, C., and Ramon, G.: Présse med. **69**: 1049, 1927.
9. Friedman, E., Esserman, A. L., and Black, M. H.: J. PEDIAT. **5**: 505, 1934.

PROPHYLACTIC PERTUSSIS IMMUNIZATION

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THE use of pertussis vaccine in the prevention of whooping cough was given added stimulus by the report of Sauer[1] in 1933 on a group of 500 children, followed over a period of five years. A total of 8 c.c. (1 c.c. equals 10 billion bacteria) of *Bacillus pertussis* vaccine was given in three weekly bilateral injections of 1, 1.5, and 1.5 c.c. At that time none of the injected children intimately or accidentally exposed had contracted whooping cough during the period of observation. In a later report[2] in November, 1935, a summary of his results, together with reports of thirty-three physicians in nineteen states using the Sauer vaccine and dosage, showed protection in 92 per cent of the vaccinated group.

These studies perhaps emphasize the importance of dosages larger than had previously been employed by Madson,[3] who reported his observations of two epidemics in the Faro Islands in 1924 and 1929. Using 22 billions as his dose in the 1929 epidemic, he found sixteen times as many severe cases and a mortality thirty-three times greater in the unvaccinated group, as compared with the vaccinated group. Further, 24.5 per cent of the vaccinated individuals did not contract the disease, as against 1.8 per cent in the unvaccinated group.

Shortly after Sauer's report in 1933 a study checking the effectiveness of larger doses of vaccine on a group of preschool children in a crowded lower east side section of Manhattan was started. A preliminary survey of 100 records of children enrolled in the Jacobi-Calhoun Pre-School Clinic of the Henry Street Visiting Nurses Association revealed an incidence of approximately 25 per cent of whooping cough in this district. We were interested not only in checking the efficacy of larger doses of Sauer vaccine, but also in evaluating prophylactically the efficacy of a toxin vaccine developed by Mishulow,[4] which was being distributed by the New York City Department of Health and which had been in general use therapeutically since 1930.

OUTLINE OF STUDY

1. Children of preschool age whose histories as to previous illnesses were known from birth were carefully selected. Whenever possible, in families of two or more children, half the number were left unvaccinated as controls. The selected children were all from a very densely populated and circumscribed district, where they were in daily and intimate contact with one another during the period of observation. About half the number attended the same nursery school.

2. A vaccine developed by Mishulow, containing 10 billion *Bacillus pertussis* organisms per cubic centimeter and small amounts of a toxic

substance capable of giving the Shwartzman phenomenon in rabbits, was used. This vaccine differs from the Sauer preparation in that stock strains of proved antigenicity, grown on infusion agar plus 25 to 30 per cent of normal animal blood, were used.

3. A comparison of the intramuscular, subcutaneous and intracutaneous methods of injecting the vaccine was attempted, to determine the best route of administration. The intracutaneous route was suggested by the work of Tuft, Yagle, and Rogers,[5] who found that this method in antityphoid vaccination gave the best results. Mishulow[6] in 1932 also found a delayed but higher agglutinin response to typhoid vaccination when given intracutaneously.

4. Studies of agglutinin response to pertussis vaccine were carried out on a small number. Bleedings were taken before injections, and one week, one month, two months, and three months after the completion of vaccination. This study was in the nature of a preliminary attempt to determine the type and duration of agglutinin response to vaccination. More elaborate and complete studies by Miss Mishulow will be published elsewhere.

5. White blood counts and differential counts were likewise made on this small group in an attempt to check the characteristic lymphocytosis reported by Sauer.

6. A small group was treated with the Sauer vaccine for comparative study.

7. A comparable group of children of preschool age was observed as controls, some receiving injections of sterile milk, which was diluted to the same opacity and injected in the same volume as the vaccine, the remaining controls receiving no injections of any type.

RESULTS

Table I indicates the results of prophylactic vaccination carried out on 74 children. It will be noted that the incidence of those definitely and intimately exposed is quite high—36.5 per cent over a period of thirty months from February, 1933, to August, 1935. The actual exposure, including accidental or casual exposures, must undoubtedly have been higher in such a district as this one.

Of those receiving the Mishulow vaccine, that is, 63 children, 10 developed whooping cough, an incidence of 15.8 per cent. Six of these cases were of not more than three weeks' duration and were without the characteristic whoop and vomiting. They might easily have gone undiagnosed except for the close observation made on these children.

It is to be noted further that 6 of the 10 developing pertussis came down within four months after vaccination, an arbitrary period established by Sauer as necessary for complete immunity to have developed. Four children of this group received small doses from 9 to 22 billions, including 2 who received the vaccine intracutaneously.

In the smaller group of 11 children receiving the Sauer vaccine, one child developed whooping cough 16 months after vaccination, an incidence of 9 per cent. He had received, however, a total of only 40 billion bacilli. The combined groups of 74 vaccinated children show an incidence of pertussis of 14.8 per cent.

TABLE I

VACCINE AND METHOD	TOTAL DOSAGE IN BILLIONS	NO. VACCINATED	DEFINITELY EXPOSED				NO. IN EACH GROUP
			NO.	DOSAGE IN BIL.	MONTHS AFTER VACCIN.	CHILDREN DEVELOPING PERTUSSIS	
Mishulow				79	17	–	0
10 bil.	77-88	7	3	79	4	–	
per c.c.				77	26	–	
				75	1	+ atypical	
	67-75	10	4	75	4	–	2
				73	24	+ atypical	
				70	5 & 21	–	
				66	1	+ atypical	
Intram.				65	1	–	
51				65	2 & 17	–	
	45-66	29	10	65	2	+ mod. severe	2
				60	24	–	
				55		–	
				50	On Vacc.	–	
				50	On Vacc.	–	
				46	3	–	
				45		–	
	12-35	5	2	18	22	+ severe	
				22	18	+ mod. severe	2
Subcut.				70	4	+ atypical	2
7	65-80	7	2	65	4	+ atypical	
Intrac.	9-10½	5	2	10	3	+ atypical	
5				9	7	+ mild	2
Sauer							
10 bil.							
per c.c.				70	4 & 6	–	0
Intram.	40-70	9	3	70	5	–	
9				40	16	+ mod. severe	1
Subcut.				65			
2	20-65	2	0	20			0

The intracutaneous route of administration was quickly abandoned because of the marked local reactions and the large number of injections necessary to give a total anywhere approaching the proposed dosage. The largest single injection given intracutaneously was 0.2 c.c., and the total amount did not exceed 1 c.c. in any child.

Reactions to the subcutaneous or intramuscular injections were never severe, consisting of redness, induration, and tenderness and occasionally a low-grade fever lasting for twenty-four to forty-eight hours. In the majority of the children, the reactions were limited to slight tenderness and induration at the site of injection.

We were unable to confirm the leucocytosis and lymphocytosis reported by Sauer. The blood counts were quite variable, ranging from

TABLE II

INTRAMUSCULAR VACCINATION

DOSAGE C.C.	AGE YR.	SERIAL NO.	NORMAL BLEEDING		AGGLUTINATION PERIOD AFTER VACCINATION WAS COMPLETED										EXPOSED TO W. C.	DEVELOPED W. C.
					1 WEEK		2 WEEKS		1 MONTH		6-8 WEEKS		3-5 MONTHS			
			DATE	TITER	DATE	TITER	DATE	TITER	DATE	TITER	DATE	TITER	DATE	TITER		
			1933		1933		1933		1933		1933		1933			
6.9	3	S1	2/28	Neg.			5/16	1-80			6/13	1:40	9/19	1:40	+	No
7.9	3	S2	2/28	Neg.					5/2	1:30	6/20	1:8	8/2	1:20	+	No
8.0	3½	S6	3/28	Neg.					5/2	1:130	6/6	1:70	8/29	1:40	−	No
7.0	4	S7	3/28	Neg.	5/16	1:80					6/27	Neg.			+	No
8.0	3½	S8	3/28	Neg.	5/2	1:35			5/23	1:80	6/6	1:40	8/22	1:10	+	No
7.5	4	S9	4/4	Neg.					5/23	1:160	7/11	1:80	8/22	1:35	+	No
7.9	3½	S10	4/4	Neg.	5/16	1:120					6/20	1:75	8/1	1:60	+	No
7.5	3	S11	4/4	Neg.			5/31	Spec								
								Lost							0	No
7.5	3	S18	3/7	Neg.	5/9	1:60									+	Mild
6.9	4	S15			4/18	Neg.	5/23	Spec					7/25	1:30	+	No
								Lost								
6.3	3	S20	5/31	1-30									7/18	Neg.	+	No
Intracutaneous																
1.10	6	S3	3/6	Neg.	4/11	1:60					5/31	1:120	8/8	1:35	+	No
1.00	2½	S4	3/6	Neg.	5/9	1:60									+	Atyp.
0.90	3	S5	3/6	Neg.					5/9	1:40	6/13	1:40	8/29	1:120	+	Atyp.
1.25	3½	S12	4/4	Neg.	4/11	Neg.					5/31	1:40	7/25	1:15	+	No
1.05	3½	S13			4/11	Neg.							7/18	Neg.	0	No
Controls—Milk—Intramuscular																
7.5	5	S14	4/15	Neg.					5/23	Neg.	6/27	Neg.	8/29	1:8	0	No
7.5	3½	S16	4/25	Neg.	5/31	1:15							9/12	1:15	0	No
7.5	3	S17	4/25	1-8	5/31	1:8			6/20	Neg.			8/1	1:10	0	No

normal to an occasional leucocytosis as high as 15,000. There was, however, no uniformity in the blood counts to suggest a specific reaction. The counts were done at the same time bleedings for agglutinin studies were taken.

The agglutinin studies, as seen in Table II, although sparse, revealed in most instances an absence of agglutinins in the control bleedings with a consistent increase in the titers to as high as 1:160 one month after vaccination was completed, and an apparent falling off in the titer in the two- and three-month bleedings. This corresponds with the results obtained by Kristensen and Larsen[7] in complement fixation studies in which they found the highest complement fixation titers were obtained in the first two weeks after vaccination, with a rapid decrease in the titers thereafter. The agglutinin response to the vaccine when given intracutaneously was comparatively delayed but more sustained and reached a titer in two instances at the end of seven to twenty weeks of 1:120, which compares favorably with the highest titers found after 7 to 8 times the amount of vaccine given by the intramuscular route. The controls treated with milk diluted to the same opacity as the vaccine and given in the same way as the vaccine showed consistently negative or insignificantly low titers.

A control group of 72 children, aged two to six years, carefully selected from the same district, were followed for periods of five to nineteen months; 26 children of this group developed unquestionable whooping cough, giving an incidence of 36.1 per cent. The period of observation in this group was somewhat shorter than in the vaccinated group, which was followed as long as thirty months, and it is not unlikely that over a similar period the incidence might be even higher. Twenty-three of the 26 children in the control group developed whooping cough during a local epidemic from seven to nineteen months after observation was begun, only 3 coming down with whooping cough from one to three months after observation was started. No child was included in this group who had not been free from cough for at least one month from the time observation was begun. A comparison of the incidence of pertussis in the vaccinated and unvaccinated groups is shown in Table III.

TABLE III

	NO. OF CHILDREN	NO. OF CHILDREN DEVELOPING W. C.	PERCENTAGE	
Controls	72	26	36.1	
Mishulow Vaccine	63	10	15.8	14.8
Sauer Vaccine	11	1	9.0	

DISCUSSION

The answer to the question as to the effectiveness of the prophylactic use of pertussis vaccine must wait on its use in a large series of cases properly controlled and followed for a sufficient period of time. The

rather striking difference in the incidence of whooping cough in the vaccinated, as compared with the unvaccinated group, and the apparent amelioration of symptoms in 7 of the 11 children who did develop whooping cough certainly justify further wide-scale use of the vaccine. The exact dosage is not yet clearly established, although it appears that those receiving the highest doses were apparently completely protected, while those receiving less than 40 billions were likely to develop modified or moderately severe whooping cough.

Although the significance of agglutinins as an index of immunity is not established, it is interesting to note the response to vaccination. Assuming some relationship, it seems reasonable to believe from our studies that vaccinated children should be at least partially, if not entirely, protected against pertussis much earlier than the four-month period proposed by Sauer, and we have consequently included all cases developing after a period of one month or longer, following the completion of vaccination. This is obviously a more rigid test of a vaccine, but until the exact value of the presence of those antibodies which are measurable in the blood stream is established, the elapsed period necessary for complete immunization must remain uncertain.

The subcutaneous route of administration thus far appears to be the method of choice, and the larger doses can be easily given in three weekly bilateral injections of 1, 1.5, and 1.5 c.c. without fear of any untoward reactions. It is interesting to note the type of agglutinin response in those children who received the vaccine intracutaneously and the fact that even very small amounts given this way were able to modify the disease considerably in the two children who eventually developed whooping cough. Therefore, in spite of the rather marked local reactions, the use of the intracutaneous route either alone or combined with the subcutaneous administration should not be abandoned without further study.

On the basis of the reduction of incidence of whooping cough in the vaccinated group treated with the Mishulow[4] vaccine, it would appear that potent vaccines may be prepared of stock cultures. It has been found that pertussis cultures can be maintained in stock without loss of their original characteristics if they are grown under suitable conditions. Furthermore, Mishulow[6] reports a higher agglutinin response in a group of children injected with the toxin vaccine than in those who received the Sauer preparation. The advantage of such a vaccine for large-scale prophylactic use is important in that it eliminates the necessity for obtaining freshly isolated strains to be grown on culture media containing human blood.

SUMMARY

1. Of 74 children injected with the varying doses of pertussis vaccine and followed over a period of thirty months, 11 developed whooping cough, giving an incidence of 14.8 per cent.

2. A comparable number of controls (72) followed over a somewhat shorter period (nineteen months) showed an incidence of 36.1 per cent of whooping cough developing during this time.

3. The subcutaneous or intramuscular injection of pertussis vaccine in amounts of not less than 65 billion bacilli has apparently afforded complete protection of those children subsequently exposed or has resulted in a marked amelioration of symptoms in the few who developed whooping cough.

4. The intracutaneous route of administration, although associated with rather marked local reactions, gave an agglutinin response comparable in titer with that found in children receiving from seven to eight times as much subcutaneously or intramuscularly and even in small amounts (10 billions) was apparently able to modify the infection when it occurred.

5. The use of the Mishulow vaccine compares favorably with that of Sauer in its prophylactic effect and for large-scale prophylactic usage eliminates the necessity of obtaining freshly isolated strains to be grown on culture media containing human blood.

Miss Lucy Mishulow, of the Bureau of Laboratories, New York City Department of Health, supplied the vaccine and carried out the agglutination studies reported in this paper.

REFERENCES

1. Sauer, L.: J. A. M. A. **100**: 239, 1933.
2. Sauer, L.: Am. J. Pub. Health **25**: 1226, 1935.
3. Madson, T.: J. A. M. A. **101**: 187, 1933.
4. Mishulow, L., Mowry, I. W., and Scott, E. B.: J. Immunol. **19**: 227, 1930.
5. Tuft, L., Yagle, E. M., and Rogers, S.: J. Infect. Dis. **50**: 98, 1932.
6. Mishulow, L.: To be published.
7. Kristensen, M., and Ahrend Larsen, L.: Compt. rend. Soc. de biol. **95**: 1110, 1926.

CALCIUM AND PHOSPHORUS METABOLISM IN A CASE OF INTRACTABLE RICKETS

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WITHIN recent years cases of late rickets which did not respond to ordinary antirachitic treatment have been described. Hess[1] reported on a patient to whom 1,600 drops of viosterol had to be given daily before satisfactory healing was obtained. In cases published by Shelling and Hopper[2] some of the patients required much larger doses of viosterol than are ordinarily given in order to obtain healing. We have had the opportunity to observe three cases of this kind, and in one of them we have made a study of the calcium and phosphorus metabolism.

In rickets an enlargement of the parathyroid glands has been reported,[3-7] and increased amount of parathyroid hormone have been found in the blood.[8] In two important respects, however, the calcium metabolism in rickets differs from that in hyperparathyroidism accompanying a tumor of the parathyroids: the serum calcium in rickets is either normal or, if tetany supervenes, lower than normal, while hypercalcemia is nearly always found in the disease caused by parathyroid tumor; and, second, the urinary output of calcium is normal in rickets[9] and is high in the presence of parathyroid tumor.[10] On the other hand, the rachitic metabolism is characterized by an increased excretion of phosphorus and sometimes, although to a lesser extent, calcium in the stools.[9]

In the presence of a parathyroid tumor, the hyperparathyroidism is, obviously, the primary cause of the disease of the bones. In rickets the rôle played by the hyperparathyroidism is not known, but it seems highly probable that it is a secondary phenomenon and not a primary factor. The question arises, however, whether in the type of case under discussion here, where the rachitic symptoms do not yield to ordinary treatment, the parathyroid glands may play a more important rôle in the development of the disease than in the ordinary case. If that were so, then one might expect to find also other symptoms of primary hyperparathyroidism, such as a high serum calcium and increased calcium output in the urine.

Our chief purpose in making this study was, then, to investigate whether the metabolism of calcium and phosphorus in this case was that usually associated with rickets, or whether it presented any other features, especially those of primary hyperparathyroidism.

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METHODS

The basic diet (Diet 1) was low in calcium so that the endogenous calcium output might be approximately measured.[11] Diet 2 contained calcium and phosphorus in amounts calculated to be normal for an individual of this age. The patient received the test diets for three days or more before the collection of urine and stools was begun for each period. Each period was of six days' duration.

The composition of the food was calculated from the tables of Sherman,[12] Pattee[13] and the United States Department of Agriculture.[14] Occasional aliquots of the diets were analyzed to check the calculated values. According to our calculations, Diet 1 should contain 0.102 gm. of calcium per day, and our two analyses gave the content as 0.104 and 0.110. In Diet 2 the calculated value was 1.282 gm., the determined values 1.352 and 1.298 gm. Phosphorus in Diet 1: the calculated value was 0.850; the determined value, 0.862 gm. and 0.865 gm. In Diet 2 the calculated value of phosphorus was 1.563 gm.; the determined value, 1.554 and 1.598 gm. The nitrogen determinations gave similarly good checks with the calculated values.

Calcium was determined by the method of Fiske and Logan[15] slightly modified, phosphorus by the method of Fiske and Subbarow.[16] Both these determinations were made on the ash of stool, urine, and diet. Nitrogen was determined directly on urine, and on dried stool and diet by the method of Kjeldahl. The method of Hamilton and Schwartz[17, 18] was used for estimating the amount of parathyroid hormone in the blood.

HISTORY OF CASE

C. W., a white female child, was first seen in this clinic at the age of five years in 1931. The complaint then was marked bowing of the legs, which had first been noticed three years previously. She had been a full-term, breast-fed baby, and had cut her first teeth at eleven months and walked at eighteen months of age. Since the age of six months "she had received three teaspoons of cod liver oil daily." Presumably her development during the first two years of life had been fairly normal, and she had not been seriously ill at any time.

The bowing of the legs had first been noticed at the age of two years but had not been recognized as rickets at that time. On her first hospital visit all the long bones showed marked deformities; the roentgenogram showed typical rachitic changes in the epiphyses. A diagnosis of active rickets was made, and treatment was recommended (16 c.c. of phosphorized cod liver oil daily). After seven months of this treatment no improvement was noted, and the child was admitted to the hospital for study. The diagnosis of rickets was confirmed by biopsy, by determination of the serum phosphorus, and by further roentgenograms.

During the subsequent years, the child was constantly on antirachitic treatment in ordinary doses, but no definite improvement of the condition was ever observed. Operations were performed to correct the deformities of her legs, but these operations had no lasting result. During these years the serum phosphorus was determined ten times. The average value was 2.1 mg. per 100 c.c., with a minimum of 1.5, a maximum of 2.7 mg. per 100 c.c. The average of ten determinations of serum calcium was 10.3 mg. per 100 c.c., the minimum was 9.6, the maximum 11.2 mg. per 100 c.c.*

At no time were any symptoms observed indicating that the rachitic condition might be due to kidney disease. In November, 1934, the nonprotein nitrogen of the serum was 31 mg. per 100 c.c.; the phenolsulphonephthalein test gave 65 per cent recovery in two hours; and the concentration test showed a maximum concentration of 1.026. Renal rickets could, therefore, be ruled out.

Two tests for parathyroid hormone in the blood were made at this time. The rise in the rabbit's blood calcium was 0.40 mM on the first occasion, 0.60 mM on the

*Seven of the phosphorus determinations and seven of the calcium determinations were made during the period of metabolic study reported in this paper.

second (normal, not more than 0.30 mM). Both tests are definitely positive, indicating that more than normal amounts of parathyroid hormone were present in the patient's blood.

In December, 1934, she was admitted for the studies of calcium and phosphorus metabolism which are here reported. It may be mentioned that during the time this

Fig. 1.—Roentgenogram of left wrist in April, 1931.

Fig. 2.—Roentgenogram of left wrist in August, 1935, after more than four years of antirachitic treatment. The rachitic changes are about equally marked as in the first film.

study has been in progress (Dec. 10, 1934, to Aug. 13, 1935), no definite improvement of the rachitic process has been observed either in the roentgenogram or the value for serum phosphorus.

DISCUSSION

Nitrogen Metabolism.—The child was in positive nitrogen balance throughout the study.

Calcium Metabolism.—The patient's output of calcium in the stools and urine on the low calcium diet (Diet 1, Table I) showed little difference from the figures given by Stearns, Oelke, and Boyd[10] for normal children and by Bauer, Albright, and Aub[11] for normal adults on a low calcium diet. The calculated balance of calcium (intake minus output) was slightly negative on the low calcium diet but tended to become positive when 30 drops of viosterol were given. Considering the fact, however, that the intake was calculated from tables, not determined by analysis, the only conclusion we feel justified in drawing is that there were neither any marked loss or gain of calcium on this diet. On the diet containing a normal amount of calcium, the daily balance became definitely positive.

It has already been mentioned that the serum calcium of this patient was consistently normal, and we may, therefore, conclude that in every respect in which it was tested, the calcium metabolism was normal. The excretion of calcium in the urine was not increased; although the amounts of parathyroid hormone in the blood were greater than normal, the case presented no features typical of primary hyperparathyroidism.

Phosphorus Metabolism.—On a low phosphorus intake the phosphorus balance was consistently and markedly negative. There was an improvement when viosterol (30 drops) or sodium glycerophosphate was given, but even after this improvement had taken place, the losses of phosphorus must be considered quite marked.

When a normal intake of phosphorus was given with the food (Diet 2, Table I), the phosphorus balance approached zero, and after the addition of 100 drops of viosterol to this diet small amounts of phosphorus were, apparently, retained.

Calculating the "absorption" of phosphorus, that is, the intake minus excretion in the stools, we find that on a low phosphorus diet without viosterol, and during early viosterol administration on this diet, more phosphorus left the intestine in the stools than entered it in the food. When the phosphorus intake was increased the "absorption" improved, but only when 100 drops of viosterol were given was this improvement sufficient to cause a retention of phosphorus.

The study of the phosphorus metabolism shows, then, that the phosphorus given with the food was not at all, or only poorly, utilized. In all probability the phosphorus was not absorbed from the intestinal tract, at least not in normal amounts. In favor of this assumption is the constantly low serum phosphorus and also the fact that sometimes larger amounts of phosphorus were excreted in the stools than the amounts ingested; some of the phosphorus entering the intestinal tract with the digestive juices was, obviously, lost to the body. It should be mentioned in this connection that the patient did not have any diarrhea; to the contrary, there was a marked tendency to constipation.

TABLE I

PERIOD AND DATES	REMARKS		CALCIUM GM./24 HR.			PHOSPHORUS GM./24 HR.			
			OUTPUT	INTAKE	RETENTION	OUTPUT	INTAKE	RETENTION	"ABSORPTION"
I		Stool	0.138			1.217			
12/10/34	Diet 1*	Urine	0.042			0.325			
12/16/34		Total	0.180	0.099	−0.081	1.542	0.804	−0.738	−0.413
II		Stool	0.081			1.080			
12/16/34	Diet 1 and 30 drops irradiated	Urine	0.037			0.323			
12/22/34	ergosterol	Total	0.118	0.102	−0.016	1.403	0.850	−0.553	−0.230
12/23/34 to 1/3/35 at home on normal diet and 30 drops irradiated ergosterol per day									
III		Stool	0.074			0.788			
1/ 7/35	Diet 1 and 30 drops irradiated	Urine	0.029			0.317			
1/13/35	ergosterol	Total	0.103	0.101	−0.002	1.105	0.843	−0.262	+0.055
IV		Stool	0.075			1.434			
1/22/35	Diet 1 and 100 c.c. 5 per cent	Urine	0.017			0.645			
1/28/35	sodium glycerophosphate	Total	0.092	0.102	+0.010	2.079	1.649	−0.430	+0.215
V		Stool	0.879			1.120			
2/3/35	Diet 2	Urine	0.028			0.554			
2/9/35		Total	0.907	1.282	+0.375	1.674	1.553	−0.121	+0.433
2/20/35 to 7/31/35 at home on normal diet and antirachitic treatment†									
VI		Stool	0.850			0.896			
8/ 7/35	Diet 2 and 100 drops irradiated	Urine	0.029			0.562			
8/13/35	ergosterol	Total	0.879	1.282	+0.403	1.458	1.563	+0.105	+0.667

*Because of a tendency to constipation, 0.5 c.c. of aromatic fluid extract of cascara was given daily.

†The patient was advised to take 100 drops of viosterol daily. For economic reasons the mother at times gave 3 teaspoonfuls of cod liver oil instead of the viosterol. At other times the patient was given free samples of various concentrated preparations of vitamin D. It is probable, however, that during all this period antirachitic treatment was given, most of the time in rather high doses.

The metabolism of this case is typical of rickets, in that the chief abnormality consists of marked losses of phosphorus in the stools. Quite atypical, however, is the very sluggish response of the phosphorus metabolism to the administration of vitamin D, and it seems possible that the underlying condition is an inability to utilize this vitamin.

SUMMARY

A girl ten years old had suffered from marked rickets at least since the age of two and was not benefited by antirachitic treatment in ordinary doses.

The metabolism of calcium and phosphorus in this case was typical of rickets and showed no similarity to that found in primary hyperparathyroidism. This rachitic metabolism did not, however, respond to the administration of vitamin D in the usual manner; an inability to utilize this vitamin might, therefore, be the cause of disease in this case.

REFERENCES

1. Hess, J. H.: Am. J. Dis. Child. **42**: 488, 1931.
2. Shelling, D. H., and Hopper, K. B.: Am. J. Dis. Child. **47**: 61, 1934.
3. Erdheim: Denkschr. d. k. Akad. d. Wissensch., Math.-naturw. Klasse, Wien **90**: 363, 1914.
4. Ritter, C.: Frankfurt. Ztschr. f. Path. **24**: 137, 1920.
5. Pappenheimer, A. M., and Minor, J.: J. M. Research **42**: 391, 1921.
6. Higgins, G. M., and Sheard, C.: Am. J. Physiol. **85**: 299, 1928.
7. Stoltenberg, L.: Norsk. Mag. f. Laegevidensk. **90**: 729, 1929.
8. Hamilton, B., and Schwartz, C.: Am. J. Dis. Child. **46**: 775, 1933.
9. Hess, A. F.: Rickets, Including Osteomalacia and Tetany, Philadelphia, 1929, Lea & Febiger.
10. Literature reviewed by Barr, D. P., and Bulger, H. A., Am. J. M. Sc. **179**: 449, 1930.
11. Bauer, W., Albright, F., and Aub, J.: J. Clin. Investigation **7**: 75, 1929.
12. Sherman, H. C.: Chemistry of Food and Nutrition, ed. 4, New York, 1932, The Macmillan Company.
13. Pattee, A. F.: Dietetics, Mount Vernon, N. Y., 1929.
14. U. S. Department of Agriculture, Bulletin No. 28, American Food Materials.
15. Fiske, C. H., and Logan, M.: J. Biol. Chem. **93**: 211, 1931.
16. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**: 375, 1925.
17. Hamilton, B., and Schwartz, C.: J. Pharmacol. & Exper. Therap. **46**: 285, 1932.
18. Hamilton, B., and Higman, W. J., Jr.: J. Clin. Investigation **15**: 99, 1936.
19. Stearns, G., Oelke, M. J., and Boyd, J. D.: Am. J. Dis. Child. **42**: 88, 1931.

CARCINOMA OF THE ADRENAL CORTEX

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CARCINOMA of the adrenal cortex with its interesting symptom-complex, virilism, hirsuties, adiposity, and hypertension has been reported a number of times. Lehman[1] reported a case of adrenal tumor removed from an eleven-month-old infant in 1917, which was described as an undifferentiated tumor. Lightwood[2] recorded a case of an infant eighteen weeks old who at autopsy was found to have a carcinoma of the left suprarenal cortex. Van der Bogert[3] reported a case of a female, aged two years, with the symptom-complex of obesity, precocious development, hirsuties, voice changes, virilism, marked hypertrophy of the clitoris and external genitals, together with hypertension and cardiac enlargement. At operation a tumor mass, differentiated as a carcinoma, was removed from the left suprarenal gland. No autopsy was permitted. F. Graham Lecher,[4] in 1935, reported a case of carcinoma of the adrenal cortex in a woman thirty-five years of age, which showed all the cardinal and most of the occasional symptoms and signs recently ascribed by Cushing to an adenoma of the basophile cells of the anterior lobe of the pituitary. Hare, Ross, and Crooke[5] reported a similar case in a woman thirty-two years of age. An extensive search of the pituitary at postmortem failed to reveal any change either in the gross or microscopic sections.

The following is a report of a case presenting the interesting, complex-syndrome of virilism, hirsuties, adiposity, hypertrophy of the clitoris, precocious development, voice change, hypertension, muscular weakness, and convulsions.

The patient, a white female, aged seven and one-half years, was admitted to the pediatric service of the Jefferson Davis Hospital, Sept. 28, 1935, in a convulsive state.

She was the first child of young, healthy parents. There was no family history of mental or glandular disorders. There was no history of syphilis. Pregnancy was normal and delivery not unduly prolonged. There was no history of birth injury or injury in early childhood. She had had chickenpox, pertussis, and mumps. Her mental and structural development was normal for the first two years. When she was three and one-half years old, the parents noted that she was rather large for her age, development being more horizontal than vertical. At the age of four and one-half years hair began to appear on the body and face, and the habitus became that of the male. Pubic hair at this time was extensive, and there was hypertrophy of the external genitals. The voice deepened. Medical aid was sought at this time and treatment consisting of thyroid and whole ovary was followed by some regression of symptoms and signs. After about fifteen months of treatment there was a return of the symptoms; the family became despondent and discontinued treatment. The symptoms and signs progressed, and the child became more and more of the

masculine type. On Sept. 27, 1935, the patient ate a large supper and awoke about 4 A.M. with severe abdominal cramps. Following this she went into a generalized convulsive state (her first convulsion), and was brought to the hospital, where she was placed on the ward. She could be aroused with some difficulty. The convulsions were controlled, and the study of the case was begun.

Fig. 1.—*A*, upper left, patient at the age of three years. *B*, upper right, patient at the age of four and one-half years, front view. *C*, lower left, patient at the age of four and one-half years, side view. *D*, lower right, patient at the age of four and one-half years, back view. Note broad shoulders, thick neck, narrow hips, and thin legs.

On examination the patient was a stocky, seven-and-one-half-year-old girl with adult habitus. The height was normal. The face thick, broad, and round, and the eyebrows were thick and bushy. There was a coarse growth of hair on the chin, throat, and upper lip. An aciniform eruption was present on the face. The voice was deep and resounding. The skull was thick, with heavy bones. The neck was short and thick. The shoulders were broad with the waist, the arms, and the legs,

Fig. 2.—Patient at the age of seven and one-half years. Note the heavy hair, thick lips, bushy eyebrows, thick nose, and male type of breasts.

Fig. 3.—Patient at the age of seven and one-half years. Note the broad shoulders, narrow hips, thin legs, and the male type of torso.

thin. Fatty deposits were present around the neck and shoulders. There was extensive hirsuties and fully developed pubic hair.

The fundi of the eye were normal. The teeth showed no abnormalities. The tonsils were enlarged and cryptic and slightly inflamed, and the pharynx was mildly injected. The chest was short and wide with flat nipples resembling the male type. Areolar hair was present. Auscultation and percussion of the lungs were normal. The heart action was rapid. The blood pressure was 120/80, and there was moderate cardiac hypertrophy.

The abdominal wall was thick. No abnormal masses could be felt, nor was tenderness present. Pubic hair was fully developed, and there was a hypertrophy of the external genitals, with an abnormally developed clitoris. The clitoris was about 3 cm. long by 1 cm. thick, resembling the male penis. There was a normal female type urethra. The hymen was intact, and the vaginal orifice admitted one finger. Rectal examination was negative. Digital examination showed the uterus to be small.

Fig. 4.—Hypertrophy of clitoris and external genitals. Note fully developed pubic hair.

The extremities were thin and resembled the male type. Reflexes were normal.

Laboratory Findings.—The hemoglobin content was 80 per cent; red blood cells were 3,500,000; leucocytes, 16,000; and differential count was normal. Urinalysis was normal except for a trace of albumin. The blood Wassermann was negative. Blood chemistry: sugar, 100 mg. per 100 c.c.; creatinin 1.0 mg.; urea nitrogen, 17.8 mg.; total nonprotein nitrogen, 38 mg.; phosphorus, 2.4 mg.; calcium, 8.6 mg. The spinal fluid was clear under no increase in pressure; cell count, 10; globulin, unincreased; Wassermann test, negative; mastic test, negative. Stool examination was negative. Sugar tolerance was lowered. Kidney function was normal. Aschheim-Zondek test was negative.

X-ray examination of the skull showed a normal sella turcica. The chest plates showed some cardiac enlargement, with hilar glandular involvement. The bones showed moderate osteoporosis with a more brittle appearance than normal. Flat plates of the abdomen showed an irregular, calcified mass in the upper left quadrant. Pyelograms showed a distortion of the calyces and pelvis of the left kidney.

No therapy was begun until all studies had been completed. On October 22 an indefinite mass was felt in the left upper quadrant with a moderate degree of tenderness. After a rather copious stool the mass disappeared, and the tenderness was relieved. Muscular weakness progressed to such a point that the patient became bedridden. While in the hospital she complained chiefly of headaches, abdominal pain, and general weakness. The blood pressure remained consistently high. Exploratory operation of the left kidney and suprarenal was advised, and the patient was posted for operation. Two days before the scheduled operation she developed hypostatic pneumonia and died seven days later.

Autopsy.—The body was opened in the midline, and the organs of the thorax and abdomen were examined. The right pleura was shiny and glistening. The left pleura was covered by a purulent exudate, and there was a pleural effusion of about 100 c.c. The lower lobes of both lungs showed a hypostatic pneumonin, the left lower lobe more involved than the right. Throughout the lobes of both lungs there were multiple metastatic nodules, varying in size from pinpoint to 1 cm. in diameter. The thyroid and parathyroid glands were normal. The heart was normal in size, shape, and position. The gastrointestinal tract was normal throughout. The liver was normal in size, shape, position, color, and consistency, but in the upper portion of the right lobe there was a metastatic nodule 3 cm. in diameter, which was apparently composed of the same tissue as the nodules down in the lungs. The right suprarenal gland was small and atrophic. The left suprarenal gland was involved in a large tumorous mass involving the whole left upper abdominal gutter. The mass was very nodular, measuring 15 by 13 by 5 cm., and was well encapsulated. On section the consistency was variable, some portions being soft and necrotic and others being firm. The color was reddish with yellowish streaks and areas. The mass did not invade the left kidney but was attached to it and pushed it down into the pelvis. On section both kidneys were apparently normal. The pituitary gland was normal in size, shape, and position, and the sella turcica was normal.

Microscopic sections from the adrenal growth showed a highly cellular structure. The cells were hyperchromatic and of irregular size with a considerable number of giant cells interspersed. The arrangement was diffuse, with strands of fibrous connective tissue intervening. The nuclei of the tumor cells were highly granular with many mitotic figures. The stroma was scant and consisted of a framework of fibrous connective tissue. Necrosis was rather marked and much diffuse hemorrhage was observed. The sections from the metastatic nodules of the lung and liver showed the same histologic picture as described above, except that the sections from nodules in the lungs showed many more capillaries filled with blood than did the adrenal growth and the nodules in the liver. Sections of the pituitary body showed normal cellular structure.

COMMENT

A case of carcinoma of the cortex of the suprarenal gland with metastasis to the liver and lungs is presented. The accompanying symptom-complex syndrome of virilism, hirsuties, adiposity, precocious development, voice change, hypertension, and hypertrophy of the clitoris and external genitals associated with hyperfunction of the adrenal gland has been reported a number of times. The function of the adrenal cortex remains shrouded in mystery. Animals without the cortex die. Whether hyperfunction or hyperexcretion of the hormones of the cortex of the suprarenal gland influences the function of the other glands of internal secretion is debatable. There are cases of

adrenal adenomas which produce the symptoms described by Cushing and are attributed to adenomas of the basophile cells of the anterior lobe of the pituitary body.[6] In this case gross and microscopic sections of the pituitary failed to reveal any deviation from the normal. Sections of the ovary were normal for development. No abnormalities were found in the thymus, thyroid, parathyroid and pineal glands.

CONCLUSIONS

1. A case of carcinoma of the adrenal cortex, with a symptom-complex of virilism, hirsuties, adiposity, hypertrophy of the clitoris and external genitals, voice changes, hypertension, muscular weakness, and convulsions is presented.

2. The remaining glands of internal secretion were found to be normal.

REFERENCES

1. Lehman, E. P.: Ann. Surg. **95**: 473, 1932.
2. Lightwood, Reginald: Arch. Dis. Child. **7**: 37, 1932.
3. Van der Bogert, Frank: J. PEDIAT. **3**: 629, 1933.
4. Lecher, F. Graham: Quart. J. Med. **4**: 23, 1935.
5. Hare, Dorothy, Ross, J. M., and Crooke, A. C.: Lancet **2**: 118, 1935.
6. Loeb, Robert F.: J. A. M. A. **104**: 2177, 1935.

817 HOLMAN AVENUE

HEMORRHAGES COMPLICATING DEEP PHARYNGEAL INFECTION

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SEVERE arterial hemorrhage occurring as a complication of pharyngeal infections in childhood is usually of such sudden and dramatic occurrence that prompt and effective treatment is necessary to meet an emergency which has not been sufficiently stressed in the pediatric literature.

We have recently encountered four cases of this type, which we wish to report. Liston[1] in 1843 was probably the first to demonstrate that an abscess of the cervical region could erode the carotid artery. Gross[2] in 1871 collected cases of hemorrhage from the common carotid and internal carotid arteries caused by postscarlatinal cervical abscess.

Salinger and Pearlman[3] in 1933 were able to collect from the literature 231 instances of arterial and venous hemorrhage complicating peritonsillar, pharyngeal, parapharyngeal, and cervical abscesses. The types of abscess occurring in our patients were retro- or parapharyngeal, and the hemorrhage in all four cases was arterial. We shall, therefore, exclude from consideration other infections of the throat and neck and hemorrhage of venous origin. The hemorrhages with which we are concerned occurred as a result of erosion of important arteries due to pharyngeal infection and were not due to injury or incision of blood vessels as a direct result of a surgical procedure.

CASE REPORTS

CASE 1.—T. S., a nine-year-old boy, was admitted to the hospital on April 30, 1923, because of difficulty in swallowing, slight dyspnea, marked left cervical adenitis, temperature of 104° F., and a rapid pulse.

Previous History.—The mother stated that the child had been well until ten days prior to admission, when he complained of slight chilliness, mild sore throat, and headache. The temperature at that time was only slightly elevated. The usual home remedies were employed without any improvement. These symptoms were followed by difficulty in swallowing and cervical adenitis. A diagnosis of a left-sided retropharyngeal abscess was then made, and the patient sent to the hospital for surgical care.

The child was admitted late at night, and, since there appeared to be no immediate indication for surgical interference, it was decided to wait until morning to make a more thorough examination. During the early morning hours the child suddenly began to bleed profusely from the mouth. The amount of blood was estimated at 300 c.c. He was immediately taken to the operating room. Inspection of the throat showed a soft fluctuating mass on the left side of the pharynx when the soft palate was retracted upward. A steady stream of bright red blood spurted from

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the mouth from the location of the bleeding vessel. We were of the opinion that the hemorrhage came from the ascending pharyngeal artery. Accordingly, under local anesthesia, the external carotid artery was ligated. The bleeding immediately ceased. At the time of this surgical experience, blood transfusion was not so universally used as a substitute for loss of blood due to a severe hemorrhage. This child made an uneventful recovery.

CASE 2.—N. C., a nine-year-old boy, was admitted to the hospital on Dec. 19, 1932, because of severe hemorrhage from the nose, throat, and right ear.

Previous History.—The illness of this patient began Dec. 10, 1932, with the usual symptoms accompanying an acute upper respiratory infection. Within a few days the child complained of a mild right-sided sore throat with pain radiating toward the right ear. Examination at this time was negative. A few days later an examination disclosed a slight edema of the posterior pillar of the fauces on the right, moderate right cervical adenitis, and a bulging of the right tympanic membrane, which, when incised, discharged mucopurulent secretion. The condition the next few days remained unchanged with the exception of the swelling in the throat, which became pronounced. On December 19, without any apparent change in the condition of the child, he had a sudden hemorrhage, blood pouring from his nose, throat, and right ear. He was immediately taken to the hospital. An examination of the throat showed a large blood clot in the nasopharynx. Under gas anesthesia, the right external carotid artery was ligated and a transfusion of 350 c.c. of whole blood was given. The temperature at this time was 103.6° F.; pulse, 130; blood pressure, 134/84. During the next few days no actual hemorrhage occurred, although definite oozing was evident from the throat.

On December 24, as the boy was sitting up, there occurred a sudden severe hemorrhage from the throat, the blood spurting beyond the foot of the bed. The patient became comatose, and his pulse was imperceptible. An intravenous injection of 100 c.c. of a 25 per cent glucose was immediately given, following which the patient regained consciousness. The child was again taken to the operating room and the previous incision was opened and the right common carotid artery was ligated. No anesthesia was used, and the patient rallied immediately. A transfusion of 250 c.c. of whole blood was given twelve hours later. There was no recurrence of bleeding. The patient made a complete recovery.

CASE 3.—C. S., a six-year-old girl, was admitted to the hospital because of a severe hemorrhage from the throat.

Previous History.—When first seen, this child was found to be suffering from a right-sided retropharyngeal abscess. The abscess was opened in the usual manner, with a blunt forceps and without difficulty or accident, considerable pus being evacuated. The following day the abscess seemed to be draining satisfactorily, consequently no attempt was made to reopen the cavity. The progress was so satisfactory that it was thought unnecessary to see the child again. Three days later we were notified by telephone that the child had just had a severe hemorrhage from the throat. The child was brought immediately to the hospital, and on her arrival taken to the operating room. Under gas anesthesia the right common carotid artery was ligated. The father proved to be a suitable donor, and the child was given a transfusion of 350 c.c. of blood. The next day, to our amazement, the child had another hemorrhage of 300 c.c. of blood. She was given another transfusion of 300 c.c. of whole blood from a professional donor. Repeated examination of the throat showed no bleeding point. For the next five days the child seemed to be progressing favorably; she took nourishment and appeared interested in her toys. During the night of the fifth day a very severe hemorrhage occurred—to quote the nurse, "The blood just seemed to pour from the mouth." The amount estimated was 400 c.c. The child

was again taken to the operating room and the right external carotid artery was ligated. She was given another transfusion of 300 c.c. of whole blood. No further bleeding occurred.

CASE 4.—B. G., a five-year-old girl, was admitted to the hospital because of a sudden hemorrhage from the throat.

Previous History.—This child had been ill for ten days with an upper respiratory infection accompanied by a mild sore throat. After several days the general condition seemed to improve, but symptoms from the throat became more pronounced. The child refused nourishment because of pain on swallowing; she held her head rigidly, and a mild trismus developed. The physician in charge diagnosed a right-sided retropharyngeal abscess and made an unsuccessful attempt to open the abscess. Three days later while the child was resting, she suddenly began to bleed from the throat and lost in all about 100 c.c. of bright blood. She was immediately sent to the hospital, and inspection of the throat showed an abscess cavity on the right side of the pharynx, filled with coagulated blood. The opening into this cavity easily admitted the index finger and the transverse processes of the upper cervical vertebrae could be felt. Just below the angle of the jaw on the right side a swelling about the size of a pigeon's egg was palpable, which could easily be distinguished from the cervical glands present. It was tense, painless, and fluctuation could be elicited.

The history of the case—the spontaneous hemorrhage from the throat following a retropharyngeal abscess, the rather sudden appearance of the swelling in the right cervical region, and the abscess cavity in the pharynx filled with coagulated blood—indicated to us that an erosion of one of the major blood vessels of the neck with the formation of a false aneurysm had occurred. From our previous experience and the experience of others, we considered it in accordance with good surgical judgment to ligate the common carotid artery. Before doing this, however, we aspirated the swelling at the angle of the jaw and found it to contain fluid blood. Ligation of the common carotid artery caused this swelling to disappear, and no further bleeding occurred. The child was given a transfusion of 150 c.c. of whole blood, and recovery was uneventful.

It is of interest to note that all of the four patients here reported had had their tonsils and adenoids removed several years prior to the illness here recorded.

DISCUSSION

A brief anatomic description of the retro- and parapharyngeal spaces will aid in understanding the mechanism of these hemorrhages.

The retropharyngeal space lies anterior to the vertebral column and extends upward to the base of the skull and downward toward the posterior mediastinum. It lies between the pharynx in front and the vertebral column behind. It is enclosed anteriorly and posteriorly by two layers of fascia. It invests the superior constrictor of the pharynx and is continued forward on the buccinator muscle. Laterally it blends with the sheaths of the great vessels. There is a chain of lymph nodes on either side of the midline between the pharyngeal and prevertebral muscles. Each chain consists of a medial and lateral group of lymph nodes. The lateral group is always present in infants and young children, but it may be absent in adults. In early life the number of nodes

may vary from three to ten and in adult life rarely more than one or two in the retropharyngeal space. A group of lymph nodes lies in close proximity to the internal carotid artery in the region where it enters the carotid canal. Therefore, an infection in the retropharyngeal space might easily involve this important vessel and, by producing erosion and false aneurysm, could cause rupture and hemorrhage from this artery. The retropharyngeal nodes receive efferent lymphatic vessels from the accessory sinuses of the nose, the nasal fossae, the pharynx, the larynx, and the middle ear. Thus an initial infection arising in any of these regions could be transmitted through the lymphatics to the retropharyngeal space.

The parapharyngeal space is the region of connective tissue which is separated medially from the tonsil by the constrictor muscles of the pharynx and the parapharyngeal fascia.[4] The lateral boundary is formed by internal pterygoid muscle, the ascending ramus of the lower jaw, and the capsule of the parotid. The space extends upward to the base of the skull and downward along the esophagus and larynx into the posterior mediastinum. It is filled with connective tissue and fat, as well as important vessels and nerves. Here are found the carotid artery, the internal jugular vein, the ninth to twelfth cranial nerves, and the sympathetic nerves. There is also a rich network of small veins and numerous lymphatic nodes.

Retropharyngeal or parapharyngeal abscess is usually secondary to an infection of the upper respiratory tract, such as nasopharyngitis, acute rhinitis, tonsillitis, sinusitis, and otitis media.[5] Abscesses of these spaces occur rarely during scarlet fever or measles, though they may complicate a severe erysipelas of the pharynx. They also may be caused by an injury to the pharyngeal wall or by perforation. It has been maintained that retropharyngeal abscess never occurs once the tonsils have been removed. The four patients here reported had their tonsils and adenoids removed several years prior to the acute illness here recorded. These abscesses need not, therefore, be preceded by tonsillar inflammation, and the initial infection may have originated in the nose, pharynx, sinuses, or ears, as probably occurred in our four patients.

A point of particular interest in the cases under discussion is the mechanism of the hemorrhages. In general, it is believed that blood vessels are protected against adjacent infection by an encasing fascial sheath. The protective mechanism is somewhat different if the infection attacks a vein instead of an artery. An infection eroding through the walls of a vein may cause thrombosis within its lumen, the venous walls being strengthened by a fibrinous deposit. Thus while the infection may erode the venous wall, hemorrhage will be unlikely if thrombosis has preceded perforation. The proximity of the internal and com-

mon carotid arteries to an infection occurring in the retro- or parapharyngeal spaces has been noted in the anatomical description of these regions. Should the infection penetrate the arterial sheath and directly involve the artery, an erosion of the arterial wall may occur, leading either directly to perforation and rupture of the artery, or to the development of a false aneurysm whose walls may eventually weaken with the result of hemorrhage. Direct perforation of the arterial wall may involve any of the arteries in the proximity of the infected area. The internal carotid artery, from its anatomical position, is most often involved. Less frequently one of the branches of the external carotid artery is involved, such as the ascending pharyngeal or the ascending palatine artery. Occasionally, however, the ascending pharyngeal artery may arise from the internal carotid, and anastomose with the ascending palatine artery arising from the external carotid. Such an anomaly would lead to difficulties in diagnosis and treatment.

DIAGNOSIS AND TREATMENT

The nature and source of the hemorrhage may be of aid in determining the vessel involved. A. B. le Mesurier[6] has pointed out that when swelling of the neck and a fullness of the pharynx precede a sudden diffuse hemorrhage from the ear, which cannot be controlled by packing, the internal carotid artery probably is involved. Brauer[7] has pointed out that spontaneous hemorrhage from the ear in the majority of cases in his experience has been due to a false aneurysm of the internal carotid artery and that erosion of the aneurysm has occurred either into the eustachian tube or into the external auditory canal by way of the parotid space. Case 2 here reported is most likely an example of this type of hemorrhage. Hemorrhage from the pharynx due to direct perforation or rupture of a false aneurysm of the internal carotid artery may be characterized by several minor hemorrhages which may be followed by a severe flow, or by a single fatal hemorrhage. In the severe type of hemorrhage the blood is not coughed up or vomited, but the bright red blood is projected from the mouth with great force. In our second case the nurse was standing at the foot of the bed before the patient's second severe hemorrhage. The boy was apparently resting quietly, when without warning he suddenly aroused and bright arterial blood gushed over the end of the bed and upon the nurse before she could move to his aid. Repeated severe hemorrhages are usually indicative of the erosion of a branch of the external carotid artery. Our Case 1 is probably an example of such a condition, as ligation of the external carotid artery arrested the hemorrhage. When infection and erosion have caused a false aneurysm of the internal carotid artery, a soft smooth swelling may be present in the pharynx, causing a mass behind the tonsillar fossae or a bulging

forward of the lateral pharyngeal wall. These swellings may be semifluctuant, and occasionally a definite pulsation is noted. If severe hemorrhages as here described are not adequately treated, they will recur and cause death.

The treatment following an arterial hemorrhage complicating retropharyngeal or parapharyngeal infections demands prompt ligation of the vessel involved. If the character of the hemorrhage is severe and suggests perforation by erosion of the wall or formation of a false aneurysm of the internal carotid artery, the carotid sheath should be exposed and the common carotid artery ligated on the affected side. Ligation of the common carotid artery may produce serious consequences because of the sudden shutting off of the circulation to one-half of the brain. If the circulation could be slowly occluded, the dangers connected with ligation of the common carotid artery would be greatly lessened. However, the emergency following a severe hemorrhage demands that the artery be ligated at once. In regard to ligation of the internal carotid artery, it has been said that cerebral complications are more severe when this artery is tied than when the common carotid itself is tied because of the fact that any collateral circulation between the external and internal carotid arteries would thus be eliminated. Moreover, a more extensive dissection would be necessary in order to reach the internal carotid artery, involving an exposure of the bifurcation. If the bleeding is indicative of perforation of a branch of the external carotid artery, this vessel should be exposed and ligated. Supplementary treatment for severe loss of blood through hemorrhage, such as transfusion, use of acacia, or injection of glucose solution intravenously, and saline solutions administered by hypodermoclysis, should be given as indicated. Complications following ligation of the common carotid artery, such as hemiplegia, or multiple paralyses, convulsions, and other nervous manifestations produced by sudden loss of circulation to the brain, together with ocular and otitic symptoms in the patients who recover, may be of a permanent nature. It must be understood, therefore, that ligation of the common carotid artery is not without danger, but the desperate situation which confronts the surgeon permits him no choice; he must treat unhesitatingly the condition by ligation, when the indications for this procedure are as here stated. The common carotid artery was ligated in three, and the external carotid artery in one of the cases here presented, with no resulting complication, and we are convinced that the procedure was undoubtedly a life-saving measure.

SUMMARY

Four cases of severe arterial hemorrhage from the pharynx and middle ear, arising as a complication of retropharyngeal and parapharyngeal infections, are here reported; all of these patients recovered.

These infections originated from upper respiratory or ear infections; all of the four children here reported had previously had their tonsils removed. The erosion and the perforation of the large arteries of the neck by infection in the retropharyngeal and parapharyngeal spaces have been discussed.

Criteria for the diagnosis of the particular artery involved in the hemorrhage have been enumerated. When the bleeding has been from a branch of the external carotid artery, its ligation has been advised. In three instances of direct perforation of the arterial wall or of false aneurysm of the internal carotid artery, we have successfully ligated the common carotid artery, and in one instance in which perforation occurred in a branch of the external carotid artery, this vessel was also successfully ligated.

We have pointed out that this operation, while not without inherent danger, is imperatively indicated to prevent fatal hemorrhage.

REFERENCES

1. Liston, R.: Brit. & Foreign Med. Rev. **15**: 155, 1843.
2. Gross, S. W.: Am. J. M. Sc. **122**: 337, 1871.
3. Salinger, S., and Pearlman, S. J.: Arch. Otolaryng. **18**: 464, 1933.
4. Abt, Isaac A.: J. PEDIAT. **1**: 8, 1932.
5. Frank, I.: J. A. M. A. **77**: 517, 1921.
6. Le Mesurier, A. B.: Canad. M. A. J. **25**: 551, 1931.
7. Brauer, W.: Ztschr. f. Hals-, Nasen-, u. Ohrenh. **32**: 561, 1933

104 S. MICHIGAN AVENUE

A CASE OF GANGRENOUS VULVITIS WITH ASSOCIATED MOUTH AND RECTAL LESIONS IN A CHILD

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CASES of gangrenous vulvitis are not unusual and have been frequently reported. In the majority of the cases, however, there has been no question concerning the etiology of the condition, either infectious conditions such as diphtheria, gonorrhea, and pneumonia, or blood dyscrasias, such as purpura and agranulocytic angina, being definitely responsible for the vulvar ulcerations. The case here reported, however, does not fall into any specific etiologic category and is presented because of its many unusual features, especially its occurence in a very young child. A careful review of the literature fails to reveal a single similar case reported.

K. F., a three-year-old white child, was admitted on Nov. 14, 1934, to the children's ward of Roosevelt Hospital, service of Dr. Philip Van Ingen. Her history was that of a head cold and cough of ten days' duration, and bleeding from the vagina and rectum for four days. The blood was bright red and appeared as a constant seepage. The child's past history was essentially negative; she had been delivered normally and spontaneously; the birth weight being 7 pounds; she had been bottle fed entirely.

The physical examination revealed an acutely ill child with frontal bossing of the head, a slight nasal discharge, coated tongue, and crusted lips. The tonsils and pharynx were red and injected. There was a slight impairment of the breath sounds over the left lung posteriorly and many coarse râles were heard over both sides. The vagina was filled with clotted blood. The labia majora were red, swollen, and excoriated. On admission there were no mouth lesions other than the excoriations of the lips.

A vaginoscopic examination showed a normal cervix with no bleeding from the uterus. Bloody mucus was present in the vagina, the blood apparently seeping from the vaginal mucous membrane. There were no ulcerations of the vaginal wall. Sigmoidoscopic examination revealed a normal mucosa of the sigmoid with engorgement of the hemorrhoidal veins and small ulcerations of the lower rectum.

On the fourth day after admission, numerous white plaques were seen in the mucous membranes of the mouth, which were buccal, sublingual, and lingual in distribution and which became necrotic. They were similar in appearance to the lesion of the vulva.

The laboratory work failed to reveal the common etiologic organisms of such ulcerations. Repeated nose and throat cultures were negative for diphtheria and hemolytic streptococci. Vaginal smears and cultures were negative for diphtheria and streptococci, with staphylococci predominating and a few gram-positive diplococci present. Smears from the sigmoid and lower rectum showed no Klebs-Loeffler bacilli, no predominating organisms; cultures taken during the proctoscopic examination grew minute gram-negative cocci and *B. pyocyaneus*. Smears from the membrane of the labia showed much fungus growth and white blood cells, and cultures revealed a minute gram-negative coccus. Smears from the mouth lesions were negative for diphtheria, Vincent's organisms, and fungi, only cocci being present.

The white blood cell count was 32,900 with 94 per cent polymorphonuclear leucocytes on admission, with similar counts on later occasions through the course of the disease.

The bleeding time was prolonged, being eighteen minutes by the finger-prick method. The platelets were abundant on the blood smear. The clotting time by the capillary tube method was four and one-half minutes.

Roentgenographic examination of the chest the day after admission showed accentuation of the hilum of both sides, more marked on the right, with no evidence of consolidation.

Course.—Throughout the hospital stay, the temperature remained practically normal with only slight rises to 100.2° F. following transfusion and before death. The pulse rate, however, was accelerated and during the second week remained over 120 per minute.

There was constant oozing of blood from the vagina and rectum. The red blood cell count fell rapidly despite transfusions of 200 c.c. on two occasions, becoming as low as 1,980,000 during the second week.

The lungs remained full of moist râles, and, although there was no rise of temperature, the patient developed a bronchopneumonia, pneumococcus Type IV being cultured from the blood on two occasions.

Throughout the illness the child consistently refused to eat and took fluids poorly.

The lesion of the vulva which appeared on admission as a congested indurative process of the labia majora with superficial excoriation, gradually developed a gray membrane extending into the lower part of the vagina and fourchet. This spread to the perineum and extended into the anus about ½ inch, at which point several engorged bleeding veins were seen with small ulcerations of the mucous membrane. The vulva itself became greatly edematous and swollen, and was painful and tender.

Local treatment of the vulva consisted of heat, diphtheria antitoxin spray, warm potassium permanganate dressings, and nupercaine ointment. There was moderate improvement of the lesion with regression of the necrotising process toward the end of the illness. Death occurred on the thirteenth day after the onset of the illness.

At autopsy the essential findings were those of the mouth, vulva, and lung. The mouth revealed multiple ulcerations and fissures, and the mucous membranes were covered with blood and pus. The vulva presented a dark purple surface, and there was a smooth ulceration encircling the urethra for a depth of one inch. The membrane noted during life had regressed.

All the lobes of the lungs were involved with masses of induration from 1 to 4 cm. in diameter. On section these appeared dry, granular, and purple.

The stomach contained considerable red blood. The small intestine appeared normal; the large intestine had a reddened mucosa, and on section of the sigmoid a considerable zone appeared shaggy because of numerous small shallow ulcerations, which were more pronounced toward the anus.

The vagina contained considerable fibrin. The anterior lip of the cervix was covered by red granulations and fibrin. The uterus was small and the cavity dry, with the tubes and ovaries normal in size and shape.

Microscopic examination of the lung showed the alveoli to be solidly infiltrated with polymorphonuclear leucocytes. With gram-staining many diplococci were found, ovoid in shape, often appearing in short chains of 2-3 pairs.

A section through the genitourinary organs included the uterus, vagina, and bladder. The endometrium was normal. The epithelium of the cervix was eroded and covered with red cells. The vaginal epithelium showed only moderate erosion with slight congestion of the underlying muscularis in the proximal part of the vaginal wall.

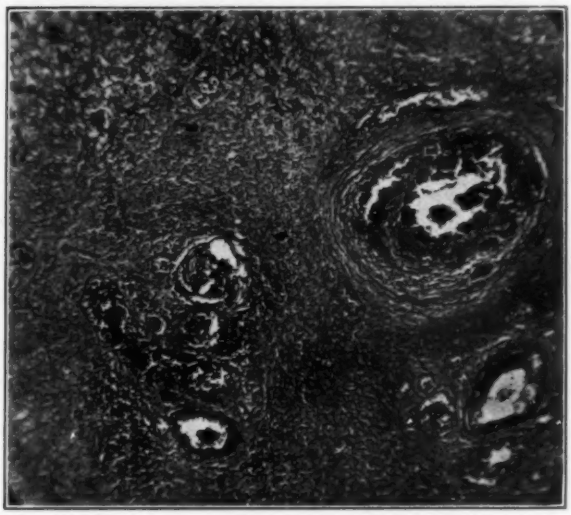

Fig. 1.—Section of the vulvar ulcer showing thrombosis of the vessels from a photomicrograph. (×60.)

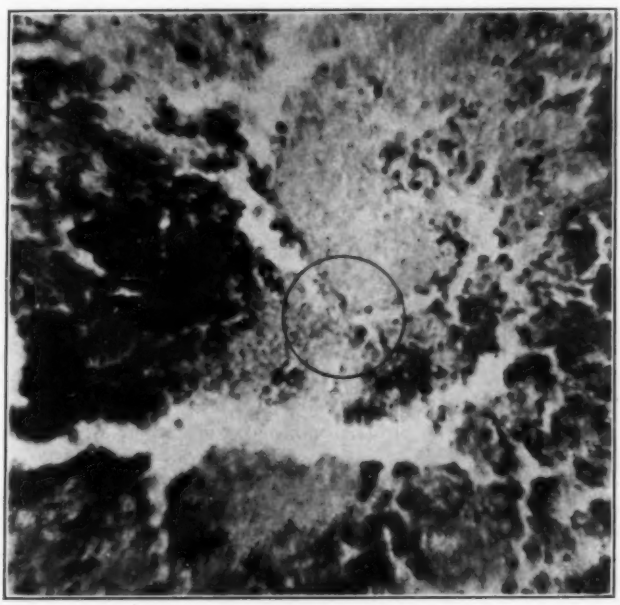

Fig. 2.—Section of the vulvar ulcer showing in the circle a clump of Gram-positive bacilli. (×1800.)

A section of the vulvar ulcer included the clitoris. On the surface the epithelium was markedly eroded. There were large masses of bacteria on the surface as well as in the glands, with massive necrosis of the superficial and deep tissues and extensive hemorrhagic and polymorphonuclear infiltration. Many of the blood vessels were thrombosed (Fig. 1). Bacterial staining showed a preponderance of gram-positive cocci which lay in large clusters as well as singly and in short chains throughout the area of necrosis. A small group of poorly defined, thin, gram-positive bacilli not unlike *B. crassus* was found lying deep in the necrotic tissue (Fig. 2).

DISCUSSION

The etiology of gangrenous ulceration of the vulva usually is not difficult to ascertain, the majority of cases being clearly associated with various vulvar infections, commonly diphtheria or septic or febrile conditions, such as scarlet fever, measles, bacillary dysentery, or typhus fever. It has been observed in cases of granulocytosis.

Wallfield and Litvak[1] reviewed the literature of 44 cases of diphtheritic vulvitis occurring before 1933; since that time there have been cases (reported by Cantrell[2]) associated with ulceration of the skin under the breast and lesions of the mouth and throat, and a case reported by Grant,[3] primary in the vagina with secondary lesions in the throat.

Gonorrheal vulvovaginitis has been known to develop ulcerations. Mention should also be made of acute phagedenic ulcers and the chronic ulcerations of tuberculosis and syphilis. These rarely, however, are confused with the acute gangrenous lesions.

Cases[4] have been reported of gangrenous vulvitis from which the fusiform bacillus and spirilla of Vincent have been obtained, but it is still a moot question whether this combination of organisms is the causative agent.

Two cases of vulvar infection by the pneumococcus have been reported, one by Dana Powell[5] in which there was extensive destruction of the vulva and surrounding tissues. In the other case reported by Trancu-Rainer,[6] there was marked congestion and edema, without ulceration.

The association of ulcers of the vulva with lesions of the mouth and throat is infrequent except in the instance of diphtheria, when on careful search the bacterium usually is isolated from the throat.

Rather an extensive literature has recently been built up on the subject "ulcus vulvae acutum" since the original paper of Lipschütz[7] in 1913 describing the association of this ulcer with mouth lesions and the finding of the *Bacillus crassus* as the etiologic factor. In 1932 Wien and Perlstein[8] reviewed twenty-nine cases of combined vulvar and mouth lesions and added a new one. Since that time cases have been reported by Matras,[9] Talalov[10] (two cases), Ziserman,[11] and Scherber[12]

(two cases). This type of ulceration occurs in adults, the youngest reported patient being sixteen years old; they are chronic, recurring in nature; they involute spontaneously; and the *Bacillus crassus* is isolated from the vulvar lesions.

Lipschütz reported 51 cases in which the lesions occurred only on the vulva; since that time there have been many cases observed of the local lesion without accompanying mouth ulcerations.

The *Bacillus crassus* has not been isolated from the mouth ulcerations except by Talalov who also recovered them from axillary lesions. In nine cases reported by Wien and Perlstein and in subsequent cases of Matras and Talalov, the *Bacillus crassus* has been isolated from the vulva.

In the case presented, repeated cultures of the mouth and vulva failed to show any of the usual bacteria found in the past as the etiologic factor. It is believed that the Klebs-Loeffler baccillus would certainly have been recovered if it had been present. The definite regression and healing that took place in the lesions points decidedly away from diphtheria as the etiologic factor. In view of the pneumococcus pneumonia and septicemia this bacterium must be considered, but cultures from the lesion should have been recovered if present, nor were any seen on microscopic section. It seems reasonable to assume that the pneumococcus infection was secondary.

The presenting symptom of severe and continuous vaginal and rectal bleeding associated with prolonged bleeding time, normal clotting time, and abundant platelets places the case in the group of purpuras due to vascular dysfunction. It is an atypical purpura in that the bleeding is limited to the mucous membranes, no purpuric spots on the skin being noted throughout the child's illness. Purpuras have been described with bleeding limited to the mucous membranes without skin manifestations. Bleeding from the gums, vagina, and gastrointestinal tract have all been observed.[13] Gangrenous forms of purpura are extremely rare but do occur, reports being limited mainly to the older literature.[14, 15]

Agranulocytosis is definitely ruled out by the high degree of leucocytosis present.

We believe that the disease probably progressed as follows: Ulceration of the vulva and rectum due to bacteria normally saphrophytic occurred in a child with a hemorrhagic diathesis. The local process became gangrenous with erosion of blood vessels. Similar ulcerations appeared in the mouth. The profuse hemorrhage and toxemia lowered the general resistance of the child and pneumonia was contracted with a fatal termination.

SUMMARY

A case of ulcerative vulvitis in a child associated with mouth and anorectal lesions is presented. The possible etiologic factors are discussed, and a review of the literature is presented.

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REFERENCES

1. Wallfield and Litvak: J. PEDIAT. **3**: 756, 1933.
2. Cantrell, R.: J. A. M. A. **102**: 1295, 1934.
3. Grant, J.: Brit. M. J. **1**: 1074, 1934.
4. Schnabl, E.: Dermat. Wchnschr. **85**: 1281, 1927.
5. Powell, D.: J. A. M. A. **64**: 1239, 1915.
6. Trancu-Rainer, M.: Zentralbl. f. Gynäk. **54**: 1356, 1930.
7. Lipschütz, B.: Dermatologische Studien, 25, 1933.
8. Wien and Perlstein: J. A. M. A. **98**: 461, 1932.
9. Matras, A.: Arch. f. Dermat. u. Syph. **166**: 491, 1932.
10. Talalov, D.: Arch. Dermat. and Syph. **30**: 510, 1934.
11. Ziserman, A.: J. A. M. A. **104**: 826, 1935.
12. Scherber, G.: Dermat. Wchnschr. **99**: 1553, 1934.
13. Christian: Oxford Loose Leaf Medicine **2**: 780, 1924.
    Junghans: Zentralbl. f. Gynäk. **58**: 1874.
    Idem: Arch. f. Gynäk. **149**: 515, 1932.
14. Charon, E.: Purpura foudroyant d'une forme anormale observé chez un enfant de trois ans, 1883.
15. Vechsler-Véren, A.: Faculté de Médecine de Paris, Thèse, 1908-1909.

112 EAST SEVENTY-FOURTH STREET

INFANTILE VOMITING—ITS RELIEF BY X-RAY

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ABOUT five years ago a premature baby in our nursery had intractable vomiting from birth. Since this did not respond to any of the usual medical measures, the child became very dehydrated and jaundiced. On the third day of life an x-ray examination of the gastrointestinal tract, following ingestion of a barium meal, showed no evidence of organic pathology of the stomach or duodenum and no gastric retention or retardation of emptying. We were greatly surprised to find that after the child's return to the nursery, the vomiting ceased entirely, and prompt recovery followed.

During the next five years we noted the same phenomenon repeated several times in vomiting babies, both after x-ray examinations for various reasons and after x-ray treatments of enlarged mediastinal shadows. The improvement in the gastric symptoms was so prompt and startling that it seemed logical to suppose that the x-ray, or the barium, or a combination of the two was responsible.

With this in mind, in May, 1935, we decided to record our experiences in any further cases, keeping careful clinical records. It was decided to try first the effect of atropine and luminal sodium and then, if the vomiting continued, to experiment with both the barium meal and the x-rays. Suffice to say that the barium alone apparently had no beneficial effect. If a child received barium and was then subjected to an x-ray examination, the vomiting was relieved. Because of this we decided that the essential part of the procedure was the x-rays. Since then we have used the x-ray alone whenever we did not feel that there was an organic pyloric or duodenal obstruction.

The value of radiation in the relief of vomiting is not original with us. In 1927 Peterson and Muller[1] suggested that the effect of x-rays was due to a nonspecific protein reaction which stimulates the sympathetic nervous system, thereby inhibiting the action of the vagus. Rodick[2] suggests that the x-rays act through the nerve roots and sympathetic ganglia. Barbour and his associate[4, 6, 8] have made the most extensive study of the beneficial effect of radiation of the upper chest upon the vomiting of children with pyloric stenosis. Rubin[7] noted relief of vomiting in children receiving radiation for enlargement of the thymus gland.

Read before the Medical Society of the County of Westchester, February 18, 1936.

Most of the patients reported, however, have had some organic pathologic condition, and the vomiting has been only a concomitant condition. We find no report of x-ray treatment of those young infants who suffer from disturbing vomiting without demonstrable organic pathology. Brush[3, 5] reports the use of repeated exposures of the abdomen to infra-red rays, as an aid in controlling this type of vomiting. Because of the frequency of this condition, we feel that our small series should be reported as a stimulus to others to carry this work further both in infants and in adults.

Our procedure now is as follows. The infant is first placed on a suitable type of formula if we feel that the existing feeding is not properly adapted to the case. Some are given atropine sulphate gr. $\frac{1}{1000}$, or luminal sodium gr. $\frac{1}{8}$, or both, before each feeding. If the vomiting is not relieved in from twenty-four to forty-eight hours, the case is then referred for x-ray therapy.

The amount of radiation necessary in these cases is very small. In the earlier cases, those which drew our attention to the matter, the only radiation received was that amount necessary for fluoroscopic examination of the stomach and for the making of one or two subsequent negatives.

In the cases now reported, we gave approximately 60 to 100 r. units over the dorsal spine and corresponding paravertebral area. The factors used are: 9 inch gap (115 kv.); 5 Ma.; 10 inch S.T. distance; 3 mm. aluminum filter; one to one and one-half minutes' time. (Case 2 was treated by grenz ray as described in the case report.)

If there is a definite improvement in symptoms, nothing further is done. If, however, the vomiting increases again after a period of improvement, the x-ray treatment is repeated. In no case have we found it necessary to administer more than two x-ray treatments.

With this technic we have been unusually successful in controlling those cases of severe, intractable vomiting after feedings, which are often the bane of the pediatrician's existence. It is our belief that the x-rays act in some manner upon the pylorospasm, which is the most probable cause of the vomiting in these cases. The effect may be through the dorsal nerve roots or ganglia, producing a reflex relaxation of the gastroduodenal musculature.

We now have complete records on ten vomiting infants treated in this way. Only one of these cases had a true hypertrophic pyloric stenosis. A brief résumé of each of these cases follows.

SUMMARY OF CASES

CASE 1.—B. M., born normally May 25, 1935, weight 6 pounds 9 ounces, was in nursery for twelve days. The infant vomited a great deal both on breast feeding, whole milk formula, lactified formula, and routine thick cereal formula, with both bottle and tube feeding.

On the seventh day child had a gastrointestinal series which showed no obstruction and normal gastric emptying. The child vomited definitely less for thrity-six hours after taking the pictures. After thirty-six hours the vomiting became frequent again. On the twelfth day the child weighing 6 pounds 3 ounces and showing evidence of mild dehydration was transferred to the pediatric service.

The infant was fed on a lactified barley gruel mixture and continued to vomit after feedings; the weight remained stationary for five days. The infant given luminal sodium gr. ⅛ before feedings vomited less for the next week, and gained weight slowly. At 1 month of age the baby weighed 6 pounds 11 ounces and had been vomiting more. One x-ray treatment was then given on June 28, 1935.

Almost immediately the vomiting became greatly less, and the child gained 7 ounces in the next three days. The child then regurgitated a little for two days, then stopped vomiting entirely, and was discharged on July 17, 1935, weighing 8 pounds 4 ounces.

CASE 2.—K. T., born May 29, 1935, at Harbor Hospital, New York City, weight 6 pounds 6 ounces, vomited after practically every feeding for first two weeks. The infant was fed dryco and then a lactified evaporated milk formula. On June 14, 1935, the weight was 6 pounds 2 ounces.

The child then received three treatments of grenz ray at two-day intervals—two on the back, and one on the chest—10 cm. focus skin distance, 22 m. half absorption value in aluminum, 250 r. units per session.

The child immediately stopped vomiting and regurgitated very little. The weight began to increase on the same formula, and she weighed 6 pounds 13 ounces on discharge from the hospital on June 21, 1935.

This child has been followed since and has had no return of pylorospasm.

CASE 3.—J. C., born normally June 7, 1935, weight 8 pounds 11 ounces, was breast fed first six days with supplementary milk formula after first week. The infant vomited a great deal after feedings in the nursery. The child was discharged on twelfth day weighing 8 pounds 8 ounces.

After discharge the infant vomited after almost every feeding and cried a great deal. After readmission to the pediatric ward on June 27, 1935, the infant, weighing 8 pounds 8 ounces, was put on lactified evaporated milk formula, and still cried a great deal and regurgitated considerable milk after each feeding.

On July 1, 1935, a gastrointestinal series showed evidence of pylorospasm but no organic obstruction. The gastric emptying time was normal.

This child began to do better immediately following the gastrointestinal series. Vomiting decreased. The child cried much less and gained weight satisfactorily.

This child has been followed carefully to date and has continued to do well, with no return of pylorospasm.

CASE 4.—G. C., born July 21, 1935, delivery normal, weight 6 pounds 4 ounces, was not nursed but was fed weak milk dilutions. The infant vomited after almost every feeding. Gastric lavage before feeding showed retention of milk curds after four hours. On the sixth day the weight was 6 pounds.

One x-ray exposure was given on July 27, 1935. The child stopped vomiting immediately following the treatment and started to gain weight on the same formula and has done well since.

CASE 5.—E. C., was admitted to pediatric ward on August 15, 1935, at age of five-plus months. The history recorded a normal birth and a normal hospital period, birth weight of 7 pounds 3 ounces. The child had nursed irregularly, had gained weight satisfactorily, but had always vomited a great deal. He was seen once in the out-patient department at three months of age and was given one x-ray treatment.

The mother was advised concerning addition of solid foods to breast feeding and the child was not seen again until admission. The mother reported that there had been no improvement in vomiting following the x-ray therapy. Our social worker, however, reported that the home investigation showed the mother to be very negligent in her care of the child and that she never followed any orders accurately. The mother reported continued projectile vomiting.

On Aug. 10, 1935, child received second x-ray treatment and at the same time was removed to the grandmother's home and put in her care. No change was made in the feeding. The grandmother reported that during the five days at her home following the second x-ray treatment, the child never vomited and regurgitated only a little.

Child was admitted to the ward because of poor nutrition and anemia and also in order to observe the vomiting. During two weeks' stay in the hospital the child ate well, gained weight, and never vomited. He regurgitated occasionally during the first week but not at all during the last five days of his stay.

CASE 6.—B. D. was seen first July 27, 1935, at age of one month because of repeated vomiting after feedings with a great deal of gas and colic. She was put on a thick barley gruel feeding and given luminal sodium before feedings for several days without benefit.

On Aug. 1, 1935, she received one x-ray treatment, without any change in feeding or medication. On Aug. 6, 1935, the mother reported that the child had not vomited since treatment and had cried very little.

On Aug. 7, 1935, solid food was added in form of cereal and purée of vegetable, because of evidence of hunger. After the feeding of the solid food the child began vomiting again and cried a great deal with colic. Luminal sodium would relieve the colic and crying but did not stop the vomiting. The child was placed on simple evaporated milk formula without benefit.

On Aug. 16, 1935, she received second x-ray treatment and was admitted to pediatric ward for observation. She was put on an evaporated milk, beta lactose, and barley gruel formula. During the week in the hospital the child regurgitated very little, cried very little, and gained 7 ounces.

This child has been followed ever since and has done very well. She has always had a tendency to regurgitate some of her food but has had no more real vomiting or colic since the last x-ray treatment.

CASE 7.—B. V., born July 10, 1935, weight 7 pounds 14 ounces, nursed only five days and then was fed milk dilutions. She was discharged from the nursery on the tenth day weighing 7 pounds 12 ounces. Nursery records showed some vomiting but not severe.

After discharge from nursery the child began vomiting a great deal—after almost every feeding. She cried a great deal day and night and was tried on many different types of formula without benefit.

The child was admitted to pediatric ward on Aug. 27, 1935, weighing 9 pounds 3 ounces and was put on lactified evaporated milk formula. She vomited the first feeding taken and several subsequent feedings.

She was then given one x-ray treatment. The vomiting stopped immediately, and child took all her food well for next twenty-four hours. She had very little regurgitation but did cry considerably and was then given three doses of luminal sodium to quiet her.

She remained in the hospital for one week and gained 8 ounces. She regurgitated a little at times but did not vomit, crying very little.

This child has been followed since discharge, has done very well, and has had no return of pylorospasm.

CASE 8.—J. F., born normally Nov. 5, 1935, weight 8 pounds 4 ounces, nursed and was given supplementary feeding. He vomited after feedings from birth. The vomiting became projectile on the third day. When he was seen by us on sixth day, he weighed 7 pounds and showed considerable dehydration. He was put on a lactified formula, atropine sulphate and luminal, together with suitable measures to replace fluid loss.

Although the child did better, he continued to vomit considerably, with occasional projectile vomiting, until the tenth day. On Nov. 15, 1935, he was given one x-ray treatment.

The child stopped vomiting immediately following the x-ray treatment and gained 15 ounces in the next eight days on the same formula.

This child has been followed since discharge and has done very well with only very occasional mild vomiting and slight after-feeding regurgitation.

CASE 9.—M. J. was born Oct. 24, 1935, after difficult delivery of a face presentation, with the cord tight around the neck. Birth weight was 8 pounds 8 ounces. From birth she was bottle fed on milk dilutions with dextrimaltose. The child was seen first at the age of two and one-half months because of difficult feeding. She weighed 11 pounds and showed evidence of poor nutrition and flabby tissues. She was put on a formula of suitable strength of the same type and cereal gruel. After one week the child was admitted to the pediatric ward because of loss in weight and strength and refusal to nurse the bottle. She had taken only 6 ounces of the formula in the thirty-six hours preceding admission and was vomiting occasionally after feedings. On admission at two months and three weeks of age her weight was 10 pounds 11 ounces.

After admission the child was put on a lactified, evaporated milk formula and was fed by gavage. Immediately after assuring a complete filling of the stomach by gavage feeding, the child began to vomit after feedings. This vomiting soon became projectile in type and would occur several times each day. The child then received luminal sodium and atropine sulphate without any change in the vomiting. At the same time a bilateral myringotomy was performed to drain the middle ears, which had become infected, probably as a result of the vomiting.

After five days of repeated vomiting, the child was given one x-ray treatment. She immediately ceased vomiting although it was still necessary to feed her by gavage. The vomiting never returned, and eventually the child's appetite improved after a direct blood transfusion several days later.

The child has been followed since and has never again vomited or had any serious regurgitation after feedings, although it is still somewhat of a problem to make her eat sufficient food.

CASE 10.—D. N., whose birth history was irrelevant, was seen first at age of three months, weighing 9 pounds 5 ounces. This child had been followed in a welfare station continuously for the two months preceding admission. The net change in weight during this past two months was a loss of 5 ounces. The child had vomited projectily several times each day. He had been treated by both atropine sulphate and dietary measures without apparent benefit.

On admission he showed the typical picture of hypertrophic pyloric stenosis with malnutrition, visible gastric waves, palpable pyloric tumor, and small, infrequent, constipated stools.

He was first put on the standard thick cereal feeding, and given luminal sodium gr. ⅛ and atropine sulphate gr. $\frac{1}{1000}$ before each feeding. After three days the dosage of atropine was doubled without benefit. On the fourth day he was given a standard barium meal from the x-ray department, but no negatives were made. This had no effect upon the vomiting, and gastric lavage four hours after feeding always showed a large amount of retention.

On the seventh day he received one x-ray treatment without any change in the feeding or medication. During the succeeding three days the child vomited only once, had large, soft, yellow stools, and gained 11 ounces in weight. During the following week he vomited only three times in spite of discontinuing the luminal.

He then did very well until the twenty-first day, when he again vomited several times and showed a small weight loss. He then received a second x-ray treatment. After this treatment all vomiting stopped although the pyloric tumor could still be felt, and the gastric waves could still be seen after feeding.

He was discharged on the thirtieth day in good condition and showing only occasional regurgitation. After discharge all medication was discontinued, and the child continued to do well. At six months of age he weighed 17 pounds 3 ounces, and the pyloric tumor was no longer palpable. He was then eating well and was on a regular intermediate mixed diet with straight milk.

SUMMARY

An analysis of the ten infants treated shows:

Onset of vomiting—birth in 5 cases, two weeks of age in 2 cases, and one month of age in 3 cases.

Loss of weight preceding treatment in 8 cases.

Relief of vomiting by formula change and medication—none in 7 cases, partial in 3 cases.

X-ray therapy administered from six to sixty-seven days after the onset of symptoms.

Result of first x-ray treatment—permanent relief of vomiting in 7 cases, temporary relief of vomiting in 2 cases, no relief of vomiting in 1 case.

Result of second x-ray treatment given in 3 cases was permanent relief of vomiting in all.

CONCLUSION

1. X-ray therapy is of definite value in the control of vomiting in infancy, whether due to hypertrophic pyloric stenosis or to functional pylorospasm.

REFERENCES

1. Peterson, W. F., and Muller, E. F.: Arch. Int. Med. 40: 575, 1927.
2. Rodick, J. C.: New Orleans M. & S. J. 87: 820, 1935.
3. Brush, Clinton E.: Physical Therap. 50: 41, 1932.
4. Barbour, Orville: J. A. M. A. 97: 455, 1931.
5. Brush, Clinton E.: Physical Therap. 49: 1, 1931.
6. Barbour, Orville, and Connell, J. W.: Illinois M. J. 57: 110, 1930.
7. Rubin, Mitchell I.: J. A. M. A. 90: 1694, 1928.
8. Barbour, Orville: Arch. Pediat. 44: 314, 1927.

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EPIDEMIC VOMITING AND DIARRHEA

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DURING the month of March, 1936, a considerable proportion of the residents of Milwaukee suffered from an illness characterized by vomiting. Diarrhea was associated with the vomiting in some instances, but in many there was constipation. The disease was quite familiar to the physicians of this community as they had recognized it as a clinical syndrome for many years, but the large number of individuals affected caused considerable comment and much discussion as to the nature and cause of this epidemic illness. It was thought that a clinical report might be of interest, as very little has been written about this disease. Zahorsky,[1] of St. Louis, in 1929, published a paper entitled "Hyperemesis Hiemis, or the Winter Vomiting Disease." He mentioned that he had observed this disease for the past thirty years and believed that it should occupy a distinct place in the nosology of children's diseases. His description resembles very much the condition observed in Milwaukee.

Nomenclature.—Many names have been used to designate this disease; it has been called stomach or gastric influenza, intestinal grip, epidemic gastroenteritis, winter vomiting disease, and epidemic vomiting and diarrhea. The last designation is the only one that can really be given to this illness at the present time, as there is no proof that it is a form of influenza or grip. It is probably gastritis or enteritis or both, but this has not been proved, as the illness is rarely fatal. Zahorsky's term, "Winter Vomiting Disease," is apt, but many outbreaks are seen in the spring and fall, and occasionally it may be observed in summer.

Symptomatology.—The disease affects infants, children, and adults, but only the symptomatology of infants and children will be described. It is certainly very rare in breast-fed infants and in infants under three months, but it may be seen even then. The onset during the last epidemic was very sudden and began with forceful vomiting, repeated frequently. After the stomach was empty, the vomitus consisted of thick stringy mucus. In some instances the vomitus was bile stained, and even small amounts of blood were seen mixed with the mucus. The vomiting continued for one to five days and then subsided. Relapses were frequent and were observed from two days to two weeks after the subsidence of the first attack.

Diarrhea was observed in some instances, but constipation was present more often during this epidemic. In previous years diarrhea was observed in most patients, sometimes with vomiting and at other times without vomiting. Another prominent symptom was abdominal pain. This was usually intermittent and spasmodic and occurred just before

vomiting or defecation. Sometimes the abdominal pain was continuous and severe enough to cause the child to double up and thrash violently about the bed. The pain was usually referred to the upper abdomen, but often could not be localized.

At times there was a disquieting complaint of pain in the right lower quadrant, and it was comforting to know in some instances that children with pain in this region had had previous appendectomies. The general symptoms were prostration, anorexia, and a characteristic lethargy alternating with irritability. Recovery appeared complete after two or three days, but, as will be mentioned later, this recovery was more apparent than real with many children. Very rarely were there any symptoms of upper respiratory infection, such as nasal discharge, cough, or earache. Occasionally a head cold would precede the illness or follow it, but this was the exception. There was no permanent immunity.

Examination.—Many patients did not appear very ill. Others were prostrated and pale, with unhappy facial expressions and sunken eyes. A few appeared alarmingly toxic and dehydrated, especially after the illness had progressed a few days. There was a slight redness of the palpebral conjunctivae.

The tongue was dry and coated, with prominent red papillae. The tonsils were not inflamed, and there was no cervical adenopathy, but in many patients a slight faucial redness was observed. It was difficult to be sure that this was abnormal, and in some cases the throat was normal in all aspects. The heart and lungs were always normal. The abdomen was sometimes slightly distended and sometimes sunken. On palpation peristaltic gurglings were often observed. There was never any evidence of spasm or rigidity, and the muscle walls were soft, except in certain instances in which the children resisted abdominal examination. The question of appendicitis was often considered and was a very important problem. Any definite tenderness or spasm in the right lower quadrant should rule out this epidemic vomiting disease. In most instances the patients were not exactly sure "just where it hurt" but complained bitterly of pain in the abdomen. The diarrheal stools were usually yellow in color. The odor of the stools was foul and putrefactive. There was rarely any excoriation of the buttocks. The diarrhea was considered to be putrefactive as distinguished from a fermentative diarrhea, in which the stools have a sour odor and produce extensive excoriation of the buttocks. Zahorsky writes that the microscopic examination of the stools in the winter vomiting disease rarely shows cells, but generally in summer diarrhea examination shows a massive cellular content of the stools.

The temperature at the onset of the illness was usually slightly elevated (99 to 100° F.). Some children developed a much higher temperature on the second day (102 to 104° F.), which subsided after one or two days.

Laboratory Examinations.—The urine was often normal. Some dehydrated patients had a concentrated urine with a trace of albumin. Acetone was rather commonly present, but very rarely was diacetic acid found. The microscopic examination was negative, except that a few casts might be found when the urine contained albumin. The blood count was not distinctive and was frequently within normal limits. A slight leucocytosis was present in a few cases. Leucopenia was not observed. Nothing unusual was found in the differential count. Zahorsky found the leucocyte count to range from 7,000 to 13,000 in his cases. Blood counts were not often required in this disease as seen in the home, but they were obtained from a few of the sicker patients. It was not considered necessary to investigate the question of acidosis or alkalosis although it is possible that severe vomiting with the loss of chlorides may have produced temporary alkalosis in some of the more severely ill patients.

Relapses and Second Attacks.—As has been mentioned, relapses were seen rather frequently. The patient would seem to have recovered from the vomiting and diarrhea, and then after a day or two or a week or two, the illness would recur. In previous years I had observed children who had several attacks during a period of weeks. When the illness reappeared after an interval of a week or ten days, it was a question whether the second attack was a relapse or reinfection. This question cannot be answered at this time, but I believe that in most instances it was a relapse. It would seem that there is a subacute stage which may follow the acute vomiting or diarrhea. There are children who have had this disease in the acute form and apparently recover. However, they are not well, in that they are tired and irritable and have poor color. There may be occasional vomiting, or they may have two or three loose stools daily which are light yellow in color and putrefactive in odor. There is a frequent complaint of colicky abdominal pain, often after food is eaten. These children may be relieved in a short time with a high carbohydrate and a low protein and fat diet. Untreated they recover completely after two or three weeks.

Treatment.—Since the disease is self-limited and nonfatal, recovery nearly always occurs. The severe vomiting is not relieved by any measure that I am familiar with. The best procedure would seem to be the giving of small amounts of liquids if the patient desires to drink. The liquids may consist of water, weak tea, carbonated beverages, cereal gruels, and fruit juices. I do not believe that milk or broth should be given. If the patient can abstain from food or water for a few hours, he will be relieved from his nausea more quickly. Drugs are of very little value. Sedatives or opiates may be of some use but are usually not given for fear that some serious abdominal disease, especially appendicitis, may be present. Heat to the abdomen is often very soothing to the patient. After the subsidence of the vomiting, a high carbohydrate diet is given

for a few days. Milk, eggs, meats and soups are omitted. Starches and sugars are given freely.

The diarrhea usually responds promptly to this regime. The apple diet has been used in a few cases with diarrhea with very good results. Paregoric may be given for diarrhea and colicky pain after the illness has lasted for a few days and the diagnosis is certain, but as has been mentioned it is best not given at the onset.

If the patient is apparently well, a general diet is introduced gradually. Some children will relapse when milk is taken, and they are again given the high carbohydrate diet for a day or two. If the patient is seen in the subacute stage, he is placed on the high carbohydrate diet and in two or three days, his condition improves. The rationale of the high-carbohydrate, low-protein and low-fat diet is demonstrated chiefly in the treatment of diarrhea—the relapses often seen when the patient is given large amounts of proteins and fats after he is considered recovered—and in the beneficial effect of this diet in the subacute stage of this disease.

Etiology.—This is entirely in the realm of speculation at the present time. The disease is undoubtedly infectious and contagious and apparently has a short incubation period of one to three days. Whether the organism is a bacillus or a virus is unknown. Although it is apparently not associated with the common cold or acute respiratory infections seen during the winter months, some believe that the disease begins as a mild throat infection and the gastric and intestinal symptoms are complications. The drinking water has been accused, but the usual bacteriologic examinations do not agree with this theory. If this disease is due to a virus, it may not be demonstrated by the usual bacteriologic examinations. The occurrence of this illness in widely separated communities is also evidence against the contaminated water theory. It is very likely spread by direct contact, as it may be seen in infants who received nothing but sterile food and water. Zahorsky considers four theories: (1) frozen milk, (2) peculiar manifestation of influenza, (3) respiratory infection (common grip), (4) toxic substance in milk, cream, or butter, but does not accept any of these theories. It may be possible that this is a definite clinical entity with a specific causative agent, but at present we can only confess our ignorance of the etiology.

CONCLUSION

Epidemic vomiting and diarrhea has been described. The etiology is unknown. A high-carbohydrate, low-protein and low-fat diet, after a period of starvation, appears to be of benefit in the treatment.

REFERENCE

1. Zahorsky, John: Arch. Pediat. 46: 391, 1929.

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CONGENITAL OBSTRUCTIVE JAUNDICE

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THE question of jaundice due to congenital obstruction of the bile ducts is one essentially of the degree of obstruction. In most patients who live any length of time, a certain amount of bile is found in the gastrointestinal canal. With complete obliteration of all the ducts, the outcome is necessarily fatal and in the majority of such cases reported, fatal termination has occurred in several weeks or several months. The following case is presented because of the unusually long duration of life and the absence of hemorrhages in the presence of complete biliary obstruction.

Case reports of congenital obstructive jaundice have been reviewed by Lavenson,[1] Deaver,[2] Holmes,[3] Croswell,[4] Rosenberg and Judd,[5] Ladd,[6] Scriver,[7] Parsons and Hickman,[8] Cole and Whittle.[9] In Lavenson's series from the literature, there were only three patients out of sixty-two who lived longer than three months. Two of these three patients died before the age of nine months, and one died before the age of eleven months. Deaver[2] reported a child who attained the age of one year and twelve days. In this case the jaundice appeared at the age of six weeks, making the duration of obstructive jaundice, clinically, ten months, three weeks, and five days. Holmes,[3] in a large series of cases, showed that surgical intervention is doomed to failure in 84 per cent of patients because of anatomic anomalies in which sufficient structure was not present to permit of creation of a passageway for the bile to reach the intestinal tract, or because the degree of hepatitis present was so marked that the radicles of the intrahepatic bile ducts were so obstructed that an adequate external outlet for the bile was not apparently present.

REPORT OF CASE

Baby R. R., female, ten weeks old, was first seen on March 11, 1935. The presenting complaint was jaundice since birth.

Past History.—The family history was essentially negative. There were five other children living and in good health. The family history was negative for syphilis, tuberculosis, familial jaundice, or any chronic disease.

The birth weight was 7 pounds 10 ounces. The delivery was normal and spontaneous. The baby was breast fed and took her feedings well. Neither cod liver oil nor orange juice had been included in the patient's diet.

Present Illness.—A yellowish discoloration of the skin and mucous membranes was noted soon after birth. The jaundice became intense on the second day and continued to increase in severity. The gain in weight had been slow. The bowel movements had been regular with pasty and clay colored stools. The urine was a deep brown color. There had been no vomiting, diarrhea, fever, or hemorrhages.

From the Departments of Pediatrics and Surgery, Women's and Children's Hospital, Toledo.
Reported by courtesy of Dr. J. F. Frye.

Physical Examination.—The patient was a poorly nourished but active baby showing a striking deep yellowish discoloration of skin, sclerae, and mucous membranes. The skin was dry and inelastic. There was a loss of the normal muscle turgor. The head and neck showed no abnormalities. The heart and lungs were normal. The liver margin could be distinctly felt three fingerbreadths below the right costal margin. The liver edge was firm and smooth to the examining hand. The remainder of the examination was essentially negative. There were no hemorrhages visible. The infant's weight at time of examination was 8 pounds 4 ounces. The temperature was 98° F. (rectally).

Laboratory Findings.—The blood findings after the infant was admitted to the hospital showed: hemoglobin, 76 per cent; erythrocytes 3,480,000; leucocytes, 22,600; platelets, 288,000; polymorphonuclear neutrophiles, 53 per cent; lymphocytes, 40 per cent; mononuclears, 5 per cent; eosinophiles, 1 per cent; basophiles, 1 per cent. Urinalysis showed a specific gravity of 1.012, acid reaction, negative reactions for albumin and sugar, four-plus bile reaction, and amorphous urates in the sediment. The blood Wassermann test was negative. The bleeding time was 3 minutes; the clotting time was 4 minutes. The erythrocyte fragility test showed hemolysis beginning at 0.41 per cent sodium chloride with complete hemolysis at 0.28 per cent sodium chloride. The immediate direct van den Bergh reaction was positive. The icterus index was 71.

The feces were consistently clay colored and gave a negative reaction for the presence of bile.

Course.—In the hospital the infant was placed on a high carbohydrate diet and given liver extract (Armour) 30 drops, four times daily. Orance juice and cod liver oil were included in the diet. There was a slow gain in weight during the period of hospitalization. The feedings were well taken, and the bowel movements were regular. On the fourth day of hospitalization, a laparotomy was performed by one of us (F. O.) with the hope of finding a biliary obstruction that might be relieved by surgery.

Under ether anesthesia the abdomen was opened through an upper abdominal paramedian incision. The organs were all bile stained, and there was a small amount of free yellowish fluid in the peritoneal cavity in excess of normal. The liver was enlarged about 3 cm. below costal margin with a sharp edge, and numerous fibrous markings on the surface. On the under surface the gallbladder presented as a normal shaped viscus about the size of an unshelled almond. Exploration for ducts revealed complete absence of cystic, hepatic, and common ducts. There was a short fibrous cord at the end of the neck of the gallbladder which had no apparent connection with the structures in the region of the hepatic artery and portal vein. Aspiration of the gallbladder produced colorless mucus. A small piece of tissue was taken from the liver for biopsy. Bleeding during the operation was not excessive.

Biopsy section (Fig. 1) showed pale liver cells with prominent nuclei and yellow bile-stained cytoplasm. The cells appeared in normal arrangement but were compressed and overlapping. The entire lobular outline showed a contracted border. The interlobular tissue was increased in amount and showed extensive lymphocytic and leucocytic cellular infiltration. There was a multiplication of bile ducts, numerous biliary calculi, and thickened blood vessels. The diagnosis was obstructive cirrhosis of the liver.*

The patient was discharged from the hospital ten days after admission. Her general condition appeared somewhat improved. The weight was 8 pounds 10 ounces.

On Aug. 7, 1935, nearly five months after the abdominal exploration had been performed, the patient was again examined. The interval history revealed little in addition to the fact already known about the case. The child had maintained a fair degree of health but was less active. She took her feedings well and continued to

*Report by Dr. S. S. Hindman, pathologist.

show all the signs of a complete biliary obstruction. On examination she now showed a more intense jaundice. The child appeared irritable but at times was apathetic. The skin and mucous membranes were a deep greenish bronze color. There was a scattered fine papular eruption over the body and evidence of pruritus. The weight was 10 pounds 7 ounces. There were marked malnutrition, marked dehydration, and loss of normal tissue turgor. There was no evidence of hemorrhagic diathesis. The liver edge was firm and could be felt four fingerbreadths below the right costal margin. The spleen could not be palpated. The remainder of the examination was essentially unchanged. A stool specimen was clay colored and showed a negative test for the presence of bile. The urine was a deep brown color and showed a four-plus bile reaction but was otherwise negative. The regular seven-month dietary additions were prescribed. The continuance of a high carbohydrate diet and liver extract was advised.

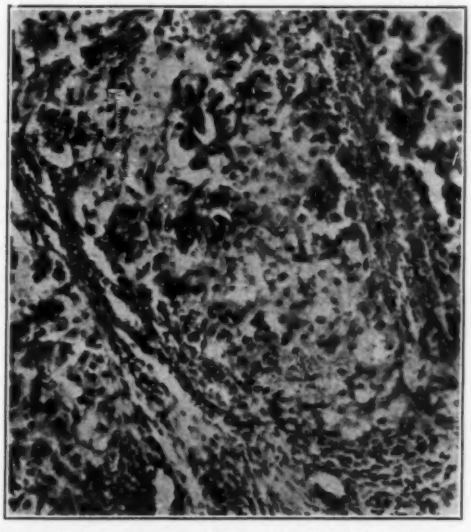

Fig. 1.—Biopsy from liver showing increase in interlobular tissue, multiplication of bile ducts, biliary calculi, and interlobular cellular infiltration.

Readmission to Hospital.—On Dec. 26, 1935, the patient was readmitted to the hospital intensely jaundiced and with bilateral bronchopneumonia. The liver was enlarged and could be felt two handbreadths below the right costal margin. The edge of the spleen could be palpated with some difficulty because of the marked abdominal distention. The physical and laboratory examinations were similar to the earlier reports of a complete biliary obstruction. The icterus index was 82 . The patient expired on the third day of hospitalization.

The essential findings at autopsy showed congenital obliteration of the cystic, hepatic, and common bile ducts; congenital obstructive cirrhosis of the liver; chronic passive congestion of the liver and spleen; bilateral bronchopneumonia.

The liver weighed 600 gm. The cut surface was a deep greenish red to reddish black color and was coarsely lobulated. The central veins were conspicuous, and there were prominent fibrous streaks throughout. The gallbladder was normal in size and shape, thin walled, and contained a small amount of thin flocculent fluid. Dissection showed that the cystic duct was a fibrous cord with no definite termination. Fibrous structures in the tissue around the hilus of the liver appeared to resemble ducts, but microscopic examinations did not show any definite duct structure.

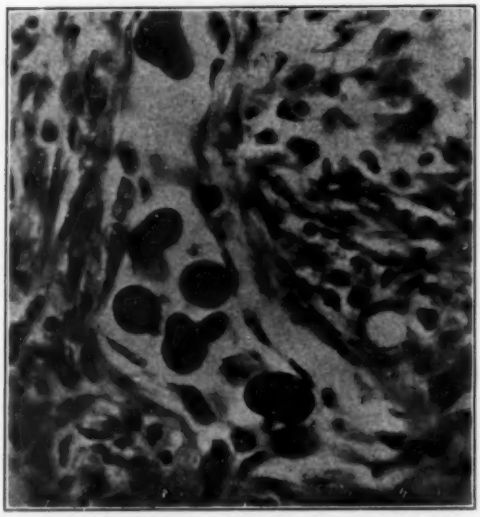

Fig. 2.—Section from liver obtained at postmortem showing marked interlobular fibrosis, increased interlobular cellular infiltration, and numerous biliary calculi.

Fig. 3.—High power photomicrograph of liver section showing biliary calculi, numerous fibroblasts, and evidence of new connective tissue formation.

Microscopic examinations of sections of the liver (Figs. 2 and 3) showed a marked increase in interlobular tissue. The fibrosis was widespread. There were more and larger biliary calculi, many of which showed a distinct concentric formation. The lobules were smaller and more contracted than those observed in the biopsy specimen. There was a more marked cellular infiltration and a lesser degree of multiplication of bile ducts. The diagnosis was obstructive cirrhosis of the liver.

COMMENT

It has been generally agreed that a high carbohydrate diet aids in the protection of the damaged liver and reduces its metabolic work. Whipple, Opie, and others have shown that livers containing an abundance of glycogen are far less susceptible to certain toxic agents than glycogen-poor livers. Mann[10] has shown that dogs with completely obliterated biliary outflow will survive up to ten or thirteen months provided they have been maintained on a high carbohydrate diet. Such animals, however, will survive only a few months if maintained on meat diets. In the case reported, a high carbohydrate formula and supplementary foods high in carbohydrates were given.

A positive test for the presence of bile in the stools of complete biliary obstruction may occur. There is a possibility of bile-stained intestinal mucosa sloughing sufficiently to appear in the feces and to stain them.[5] The case reported at no time showed any evidence of the presence of bile in the intestinal canal. The findings at the time of the laparotomy and finally at autopsy conclusively showed a complete biliary obstruction and a nonfunctioning gallbladder due to congenital causes.

A review of the literature on congenital obstructive jaundice reveals that hemorrhagic manifestations appear in all cases. It is of interest to note that our patient showed no evidence of hemorrhage after being jaundiced nearly twelve months. Ottenberg[11] has pointed out that the subject of hemorrhagic diathesis in jaundice patients is at present in a very unsatisfactory state. No one has as yet discovered the real mechanism of the hemorrhagic tendency in jaundice.

SUMMARY

A case of congenital obstructive jaundice in a female child, dying at the age of eleven months and twenty-nine days of age, is reported. Exploratory laparotomy done when the patient was ten weeks old revealed a congenital obliteration of the cystic, hepatic, and common ducts, and a nonfunctioning gallbladder. Biopsy of the liver at the time of the laparotomy and pathologic changes in the liver at autopsy are described. The long duration of life in the case presented is ascribed in part, to the hepatogenic functions of organs other than the liver and to a high carbohydrate diet.

REFERENCES

1. Lavenson, R. S.: J. Med. Research **8**: 61, 1908.
2. Deaver, J. Montgomery: Am. J. Dis. Child. **46**: 356, 1933.
3. Holmes, J. B.: Am. J. Dis. Child. **11**: 405, 1916.
4. Croswell, C. V.: J. Tennessee State M. A. **27**: 316, 1934.
5. Rosenberg, Lester, and Judd, George: Arch. Surg. **8**: 2339, 1929.
6. Ladd, W. E.: J. A. M. A. **91**: 1082, 1928.
7. Scriver, B.: Canad. M. A. J. **27**: 517, 1932.
8. Parsons, L. G., and Hickman, Evelyn: Am. J. Dis. Child. **31**: 461, 1926.
9. Cole, Leslie, and Whittle, C. H.: Brit. J. Child. Dis. **26**: 258, 1929.
10. Mann, Frank: J. A. M. A. **104**: 371, 1935, and Personal Communications.
11. Ottenberg, Reuben: J. A. M. A. **104**: 1681, 1935.

316 MICHIGAN STREET

Critical Review

THE NEWBORN

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IN PREVIOUS reviews[1, 2] it was pointed out that there was need for uniformity of definition of such terms as "live birth," "stillbirth," "prematurity," "viability" and "abortion," before authentic interpretations could be made of the statistics accumulated by various institutions or states. During the past year or two some progress has been made in this respect through the rather independent efforts of committees appointed by several national societies, chief among which have been the Committee on Child Health Relations of the American Academy of Pediatrics, the Committee on Neonatal Mortality and Morbidity of the American Pediatric Society, a subcommittee of the American Public Health Association, and the American Committee on Maternal Welfare. In general, then, there are three groups, the public health men, the obstetricians, and the pediatrists, working practically independently toward the same end. The intimacy between maternal and neonatal death rates, as evidenced by the stubbornness with which both resist attempts to reduce them, indicates the need for closer cooperation between obstetrician and pediatrist if the most satisfactory solution of the problem is to be brought about. For this reason it seems unfortunate, indeed, that the several groups cannot appoint representatives to serve upon a joint committee whose function shall be to correlate the ideas of these groups and to serve as a liaison between them. In this way uniform definitions can be formulated which will be of inestimable value in serving to standardize statistical reports coming from various parts of the country and thus make them more readily comparable. As it is now, there is such complete variance among the states in respect to the definitions mentioned above that statistics derived from these sources cannot be used for purposes of reliable comparison. For instance, in regard to the period of gestation to which a stillborn fetus must have advanced before a certificate is required, two states require that all products of conception must be reported, and two have no definite ruling (Delaware and New Hampshire). Most states require that stillbirths shall be reported from the fifth month on while some require reporting only from the seventh month on. Furthermore, in five states (Colorado, Connecticut, Illinois, Nebraska, New Jersey, and the District of Columbia) a stillbirth is reported as a stillbirth while in the remaining states a stillbirth must be reported as a birth and as a death.

If such comparisons are desired at present, it will be necessary to create in the various states agencies using an arbitrary standard irrespective of the statutory definitions of the individual state. Actually there is a vital need for some such expedient in order that a correct cross-section of conditions throughout the country may be obtained. As it is at present the most reliable information comes from large

maternity hospitals in crowded centers of population. Such reports derived solely from the clinic type of patients are not representative because such patients are not representative of the nation. Again, statistics from such institutions where all patients are cared for by obstetricians depict a condition that does not maintain in the country at large, for it must be remembered that the great majority of confinements are handled by general practitioners. Thus of the approximately 2,160,000 live births in 1934 a little less than one-third (760,000) occurred in towns of 30,000 or over, where possibly there might be one or more obstetrician. Of this number probably not more than 20 per cent (150,000) were delivered by obstetricians. In the final rough analysis, then, it is apparent that probably not more than 15 per cent of the total deliveries in the United States were conducted by obstetricians. Therefore, it can be readily seen, that if an authentic picture of the true status of maternal and neonatal morbidity and mortality rates in the United States is desired new studies based upon new standards must be made. Studies of this nature are essential if procedures adaptable to the general practitioner, who delivers most of the babies, are to be evolved. Certainly methods used in maternity hospitals, while admirable in many respects, cannot be used always in general practice, and in some instances should be prohibited rather than urged. Advocation of the general adoption of some of these measures has, undoubtedly, been due to the inability of many teachers to realize that some of the obstetric maneuvers or methods of analgesia and anesthesia, which may be suitable to the well-regulated maternity hospital, cannot help but be harmful in the hands of those who have neither the skill nor armamentarium to carry them out in general practice. Until this is realized and there is a shift from the complicated to the simple type of procedure both the maternal and neonatal rates will fail to drop.

While reduction of the neonatal mortality rate cannot help but go hand in hand with any material reduction in the maternal mortality rate, it would seem a little more fitting if obstetricians were to consider the welfare of the newborn more specifically in conjunction with maternal welfare than is done at present. It is suggested, therefore, that the American Committee on Maternal Welfare should increase its membership to include those interested in neonatal welfare as well. The subordinate state committees of this organization could then serve more satisfactorily in these two closely related fields than if two separate committees were formed. Furthermore, such a state committee could readily cooperate with the Maternal and Child Health Program of the Social Security Act, perhaps in an advisory manner as is being done at present in Utah. In this way the duplication of time and effort of several committees could be dispensed with to the benefit of everyone concerned.

While a great deal is known regarding the gross mortality during the different age periods in man from birth on, such is not the case with the death rate during the intrauterine period and especially the early part of it. A few attempts have been made to estimate the mortality rate of the antenatal period, but, owing to the difficulty of obtaining accurately the abortion rate, the figures published are inaccurate and will continue to be largely speculative. In a large group of private patients Grier[3] found that the spontaneous abortion rate was 11 per cent and that over 16 per cent, or one out of six, of the mothers consulting him about confinement did not receive a live baby. Naturally these figures are not high enough but they are of value in pointing out

that in an obstetric practice among mothers desiring babies the fetal mortality was startlingly high. Using a method which at best could not be more than speculative, Taussig[4] estimated that one in four pregnancies resulted in abortion with variations of from one to five in the rural districts to one to two and one-half in the urban districts. Pfaundler[5] has published a most interesting chart of the mortality from conception to the tenth month of postnatal life. This is perhaps one of the best interpretations of its kind in existence at the present time. This chart shows that during the first months of gestation the mortality rate is exceedingly high, dropping rapidly until at the fifth month it is at the same level as that of the neonatal period. After the fifth month the rate is much lower, approximating that found after the third month of postnatal life. During the first postnatal month, owing to the damaging effect of labor, there is a quick rise followed by a rapid drop. The various attempts to estimate the gross mortality rate from conception on brings out very clearly the fact that our knowledge about the mortality rate of the intrauterine period of life is indeed scant. It does fit in with the suggestion that it is highly probable that the conception rate is more or less static and that any fluctuation in the birth rate is governed by changes in the abortion rate.[6] In other words, our declining birth rate is not so much due to lack of fecundity as to the increase in abortions, to which must be added also the increased use of contraceptives.

Since it is practically impossible to determine the abortion rate, the national and state bureaus of vital statistics have of necessity scrupulously avoided this factor and their rates have been based upon the one denominator which can be ascertained with a close degree of accuracy, namely the number of live births. Infant deaths under one year of age including neonatal deaths and stillbirths are all computed from live births. While there is no doubt that this method is the only one to be used at the present time by such bureaus, nevertheless, it does not give a true picture of the gross fetal death rate. Special studies of smaller and more intimate groups are needed to help get a more accurate conception of the gross mortality rates. In many of the statistical reports published by different observers, the term "corrected mortality" is used. It is an unfortunate term which, save perhaps in exceptional instances, should be discarded for it tends to mislead the reader. Another criticism of many of the numerous reports is the failure upon the part of the author to make statistical interpretations. In all reports of this nature the significance of percentages should be calculated statistically and the tables should indicate that this has been done.

Realizing full well the present impossibility of vital statistic bureaus making computations except upon live births, the reviewer continues to feel the need for further research into the gross fetal mortality rate as computed from total births. What we desire to know after all is how many conceptions fail to produce live offsprings and the underlying causes of such failures. The true condition of affairs is masked when computations are based upon live births, and there is a tendency upon the part of all concerned to interest themselves little or not at all in the most obscure but greatest causes of intrauterine death. With this idea more or less in mind some attempts have recently been made to draw a base line of gross fetal mortality which could be used temporarily as a standard to go by. Clifford[7] has endeavored to do this by publishing

the record of the Boston Lying-In Hospital for 60 years basing his rates upon the total number of births.

While it is desirable to study the gross mortality rate in this manner, it must be conceded that for the time being, at least, this cannot be achieved with any degree of success. Therefore, such endeavors should be attempted only as special studies and our maximum efforts should be spent upon trying to emphasize the necessity of uniformity in definitions and bases for statistical analyses.

The following outline is offered as a means by which uniformity can be brought about in classifying and recording mortality from conception through the neonatal period:

Mortality rate (per 1,000 live births).

1. For stillborn infants.
   a. Rate for abortions.
   b. Rate for prematurely born infants.
   c. Rate for full-term infants.
2. For liveborn infants (neonatal rate).
   a. Rate for prematurely born infants.
   b. Rate for full-term infants.

As a corollary to this, it is necessary to have a clear understanding of what the various terms mean. The following list of definitions has been evolved largely by a committee of the American Public Health Association and has been endorsed by the Committee on Neonatal Morbidity and Mortality of the American Pediatric Society:[8]

Live Birth.—A liveborn infant is one who shows "any evidence of life after complete birth." *Evidences of life* are breathing, action of the heart or movement of a voluntary muscle. *By birth or completion of birth* is meant the instant of complete separation of the entire body (not body in the restricted sense of trunk but the entire organism including the head, trunk and limbs) of the infant from the body of the mother whether or not the cord is cut or the placenta detached.[9]

Stillbirth.—A stillborn infant is one who shows no evidence of life (no breathing, no action of heart, no movement of voluntary muscle) after complete birth. Unless gestation has advanced to the fifth month the product of pregnancy need not be reported as a stillbirth.

Abortion.—An abortion is any product of conception of less than twenty-eight weeks' gestation, measuring 35 cm. (14 in.) or less and weighing less than 1500 gm. (3¼ pounds). The term "nonviable," which is ordinarily used to indicate a fetus of less than twenty-eight weeks' gestation, should probably be discarded since it has no particular significance statistically or otherwise.*

Premature Infant.—An infant with a birth weight of 5 pounds 8 ounces (2500 gm.) or less, a crown-heel length of 47 cm. (18 in.) or less and a gestation of thirty-seven weeks or less, should be considered immature and, by virtue of the fact that special handling is indicated, premature. Birth weight is the most important, and probably crown-heel length and the duration of gestation should be disregarded. In re-

*If this term is used, lower limits of duration of gestation, weight, and length would be better not only clinically but anatomically. Histologically the lungs of fetuses under twenty-four weeks show an insufficient amount of elastic tissue and the formation of aveoli has just begun[10, 11] so that the possibility of such fetuses living is, indeed, remote. Clinically 95 per cent of the infants weighing under 1000 gm. at birth die, and there have been reports of only five infants surviving birth weight under 700 gm. None of these has been 30 cm. long or less.[12, 13] In 10,000 consecutive births at the Chicago Lying-In Hospital no infant weighing under 500 gm. at birth survived twenty-four hours.[14]

porting premature studies, Ylppö's grouping, which has been more or less accepted the world over, is satisfactory: (1) under 1000 gm.; (2) 1000 to 1500 gm.; (3) 1501 to 2000 gm.; and (4) 2001-2500 gm. Any weight group may be split into subdivisions if the number of cases is sufficient. Infants should be grouped according to *birth weight*, not *admission weight*.

Neonatal Period.—This term should be used to designate the first thirty days of postnatal life.

It is hoped that in the near future some satisfactory group of definitions and some scheme of reporting the mortality during this particular span of life can be agreed upon. This accomplishment alone will serve as a great aid in ascertaining more definitely some of the obscure causes of prenatal, natal, and neonatal death. Until this is done the tremendous number of statistical reports that are continually being published will be largely worthless, at least from the standpoint of their value in making statistical comparisons. In repetition it seems advisable to emphasize again that in all reports the significance of percentages should be calculated statistically.

CONGENITAL DEFECTS

When one considers the tremendous rapidity with which cell multiplication takes place during the period from conception to maturity of the fetus, it seems surprising indeed that more gross abnormalities are not observed at birth. Not all fertilized ova are of good enough quality to survive the period of gestation. Thus, it has been estimated that as many as 25 per cent of these ova succumb during the early period of development.[15] Such episodes furnish an explanation for many of the cases of spontaneous abortion. The importance of quality is not limited to uterine life, for failure to survive after birth depends not inconsiderably upon the original quality of the egg. Eggs differ greatly in such qualities as endurance and capacity for growth, and many of these differences are hereditary. With so many endogenous and exogenous factors continually at work upon the maternal organism during pregnancy, damage to the primitive cells at an early period, undoubtedly, would result in a greater incidence of defects were not these cells endowed with certain inherent powers of which we know but little. The cells have the ability to multiply at a rapid but well-governed rate and to become differentiated into special types peculiar to the various organs. With differentiation, or specialization, seems to come inhibition of growth, and the earlier differentiation appears the sooner does growth of that particular structure cease. Embryonal tissue, likewise, has the innate power to flourish at the expense of its host if necessary—a parasitic or neoplastic characteristic. The entire process follows a definite organismic plan or pattern (heredity) which can, however, be influenced considerably by environmental factors. The end-product is the result of the interplay between the more constant hereditary factors and the environmental ones. While the power of adaptation is potentially greatest in the beginning of development, actually it is utilized only slightly at this period. In other words, the end-result of the power to adapt, adaptibility, is not great at this time. As a consequence, the intrauterine mortality, especially in the beginning is exceedingly high, and then gradually decreases as the organism becomes better able to adapt itself—a situation that is maintained more or less with few fluctuations until old age is reached. When the noxious influences

are not too injurious, adaptation will take place and be facilitated by the distinct ability of fetal tissue to substitute, compensate, and regenerate, that is, its greater plastic capacity. Malformations are the result of such incidents.

By virtue of a deficiency in embryonal tissue of the necessary instruments or apparatus by which coordination between structures or organs occurs, circulatory and nervous systems, inflammation in the early stages of development does not react in the general or systemic way it does in the older organism and adult. There seems to be a failure of response to antigenic poisons which is carried over to some extent into the neonatal period. Thus, while these tissues are susceptible to infectious agents, their ability to react to them remains more or less localized and limited. In most instances this so-called immunity cannot be ascribed to the presence of antibodies, for they are definitely wanting in the fetus, but instead to the functioning of an entirely different mechanism. The increased resistance to generalized infection is the result of incompleteness of development, that is, of lack of ability of the tissues to exhibit a generalized inflammatory reaction in the presence of infection. The immune bodies that are sometimes found in the blood serum of the newborn are probably not transferred from the mother to the fetus by way of the placenta or breast milk but are formed independently in a manner perhaps somewhat similar to that which controls growth.[16] The recent investigations of McKahnn and Chu indicate that the placenta may be the spot at which immune bodies are formed.[17] It is probable, therefore, that natural or species immunity is after all not transferred from mother to child in the manner ordinarily assumed.

Numerous theories regarding the cause of some of the congenital abnormalities have been elaborated. Fetal inflammation years ago was considered one of the chief agents, and syphilis was given a place at the top of the list. With the advent of serologic procedures and methods of staining spirochetes in the tissues, our views about the part syphilis plays in the etiology of congenital malformations have changed considerably. The fact that it plays such an insignificant rôle in the causation of neonatal death or of prematurity seems to depreciate its importance in the etiology of fetal abnormalities, including congenital deafness.[18] In Clifford's report[7] comprising over 120,000 births, syphilis was credited with a death rate of only 0.52 per 1,000 births. Swanson and his coworkers[14] attributed to congenital syphilis only one death in 10,000 consecutive births. Cruickshank[19] was able to establish a definite diagnosis of congenital syphilis in but 0.75 per cent of 800 neonatal deaths. The actual part that infections of a nonspecific nature play in the development of fetal anomalies that cannot be linked with heredity is unknown. Perhaps they are more important than ordinarily thought to be the case. Certainly here is a much neglected problem.

The relationship between congenital abnormalities and maternal poisoning is not clear. The fact that the embryo is less resistant to the abortifacient poisons as well as to the heavy metals, iodine, phosphorus, and nicotine would tend to indicate that perhaps some anomalies might be the result of tissue damage by one or more of these poisons. However, if the injury were at all great, it is likely that early death of the embryo and abortion would occur. The same in all probability can be said of the possible damage to the embryo by the poisons in maternal toxemias. While the fetal mortality, including abortions, from the various toxemias has been found to be 30 per cent[20] and from maternal

diabetes over 40 per cent,[21] there are no reports that either are related to the incidence of congenital anomalies. In view of the increased use of tobacco among women a good deal has been said about its effect upon the fetus. Setting aside purely personal prejudices, so far there has been little proof offered on one or the other side that moderate or even excessive smoking affects either fecundity or fetal mortality. Even the limited number of studies that have been made regarding the effect of nicotine poisoning upon the female reproductive organs of animals have not been particularly enlightening.[22] Certainly there is little unprejudiced evidence that even excessive use of tobacco by the pregnant woman has any relationship to the incidence of congenital anomalies. Nor would one expect much effect since an amount of nicotine or carbon monoxide in the maternal blood sufficient to damage the embryo would in all probability result in death and abortion. Sontag and Wallace[23] found that later in pregnancy cigaret smoking increased the fetal heart rate slightly. They did not remark about any subsequent effects upon the neonatal heart rate. Embryonal tissue is sometimes affected deleteriously by quinine with resulting death and expulsion of the product of conception. The drug has, likewise, been incriminated occasionally as a cause of late fetal death when used to induce labor.[24, 25, 26] Accumulation of quinine in the fetal tissues was ascribed as the cause of death. Taylor[27] has reported an increased incidence of congenital deafness among infants born in malaria-infested regions, where quinine is used in large doses. In a few other instances there was some evidence that quinine used for induction of labor might have caused deafness in the newborn.[28] The drug is thought to act selectively upon the auditory nerves. Although a great deal of inquiry has been made into the effect of alcoholism upon the progeny, the results of numerous experiments have varied considerably. The consensus of opinion at present seems to be that fertility is unaffected by alcohol. Alcohol also seems to be a selective agent which destroys the weaker or more susceptible fertilized germ cells and produces superiority on the part of the surviving ones.[29] Furthermore, there is no difference in the proportion of physical abnormalities between alcoholized and control stock.[30] Therefore, there is no experimental proof to show that alcohol is an idiokinetic poison nor is there much clinical evidence to show that alcohol can produce directly in the first generation mental defects which can be transmitted as such. It is probable that alcoholism is more often a result of mental deficiency than a cause of it.[31, 32]

The destructive effect of radium and roentgen rays upon fetal tissues has been the subject of considerable interest in the past few years. The rays seem to have a particular affinity for tissues of the central nervous system, irradiation frequently resulting in the birth of anencephalic monsters or infants manifesting various anomalies of the brain and its coverings. However, abnormalities of other parts of the body have been reported. Bagg[33] has produced experimentally limb abnormalities capable of hereditary transmission. Perhaps in the instance there is displacement of the genes—the translocation theory of Muller—by the bombardment of the chromosomes by the rays.[34] Since the rays are known to have more effect upon nuclei in the process of division, embryologic tissue with so few nuclei in the resting state is especially liable to damage. Arrest of development associated with the formation of blebs and hematomas seems to be the pathologic lesions produced.[35] Focal deficiencies of this sort might explain many malformations. When

conception follows soon after irradiation, phenotypic and possibly genotypic injury may occur. When conception is subsequent to the end of the period of temporary amenorrhea caused by irradiation, no damage results.[35] Apparently the diagnostic use of roentgen rays does not have a deleterious effect upon the fetus, if used sparingly, but therapeutic irradiation after conception is so imminently dangerous to the fetus that it should be followed by abortion.[36]

Some observers have attributed certain fetal anomalies, especially those relating to the brain and spinal cord, to abnormalities of the amnion. Jansen[37] blamed pressure changes associated with shortness of the amniotic membrane for a number of these abnormalities as well as some forms of idiocy, especially the mongoloid type. So far this hypothesis has gained few supporters.

Peterson[38, 39] recently has attributed the origin of congenital anomalies to meteorologic causes, namely, variations in the barometric pressure occurring at an early period of embryologic development with a resulting disturbance of the oxidative-reductive mechanism and of the hydrogen ion concentration. This is somewhat similar to Stockard's theory[40] that an unfavorable temperature and oxygen supply affecting the fetal metabolic rate during critical phases of the development of an organ or part may account for some of the extreme degrees of fetal malformation. Peterson bases this theory upon the fact that there is a geographic increase in the incidence of certain anomalies which parallels the storm tracks of the United States. Murphy[41] was able to corroborate this in a study of congenital deformities in Philadelphia. In fact, his findings disagreed entirely with those of Peterson in that particular area.

Other factors, such as age of the mother and the number of children she has borne, seem to affect the incidence of congenitally malformed children. Murphy[42] found in a study of mothers who had at least one normal and one defective child that there were fewer defectives when the mothers were between the ages of twenty and twenty-five years. There was an increasing number of malformed children from year to year when the mothers were over thirty years old and the greatest number of defectives was born to mothers who were over forty years old. The ratio of defective children to normal children was three or more times greater after thirty years than before. In another study he and Maser[43] noted that the first four children in a family were less likely to be malformed than the subsequent progeny. These observations bring to mind the old view concerning exhaustion of germ plasm as an etiologic factor in the production of congenital abnormalities.

In general, it may be said of the various factors, mechanical, chemical, physical or otherwise, which may affect the germ cells or embryonal cells that they tend to lessen the power of adaption of these cells. By virtue of this there is an increased mortality rate, whether it is due to the primary disturbance or secondarily to a subsequent increased susceptibility to disease, and in turn through early death, race deterioration is prevented. To a considerable extent the preserving effects of our civilization work against this selective effort of nature to purify the race. With the exception of radiant energy there is little evidence to show that these other factors are truly teratogenic.[41] With Bagg's studies as a guide it may be possible in the near future to learn more about the numerous agents that underly the various developmental defects.

No doubt, nearly every physician has been confronted by the anxious parents of a malformed child with the question, "What are the chances of another defective child being born?" I wonder how many times the reply has been that lightning rarely strikes twice in the same place. According to a recent report Murphy,[45] who studied this particular question in a group of families in which there was at least one malformed child, found that such an answer was erroneous. He concluded that congenital defects serious enough to be recorded on birth certificates were approximately twenty-four times as likely to occur in families containing one congenitally malformed child as in the population at large. This problem brings up the subject of heredity.

HEREDITARY DEFECTS

The medical practitioner has been so thoroughly engrossed in the study of acquired, or what he considers acquired, disease that he has devoted but little attention to the rôle inheritance plays in some of these disorders. While he has recognized that there are individual differences in the ability of an organism to combat acquired disease and that susceptibility varies considerably in persons and families, he has been inclined to attribute these qualities chiefly to acquired factors, such as immunity. As a result of looking elsewhere, many conditions of a distinctly heritable nature have been overlooked and, if not, have engaged only cursory attention. There are several reasons why medical men have not been particularly interested in genetics. This science has gone along at such a rapid pace with its controversies and backtrackings that most of us, who have never taken as much as an elemental course in the subject, have had neither the fundamental knowledge nor the courage to attack such a chaotic and immense literature. The attempt of earlier geneticists to separate the inseparable factors, heredity and environment, and their tendency to emphasize the former perhaps at the expense of the latter has been responsible to some extent for the passiveness of the medical profession in respect to the hereditary aspect of disease. After all, the physician is primarily interested in the prevention and cure of disease, and the environmental or acquired forms have responded more satisfactorily to his efforts. In other words, the relative incurability of hereditary disease as it is known to him has been largely responsible for neglect of this field by the doctor. However, this attitude has been unfortunate, for it has limited the scope of medical practice and has not only hampered progress in medical diagnoses but also advancement in human genetical research. Genetics is such a complex subject, especially in relation to man, that there must be the closest cooperation between geneticists and physicians if any progress is to be made. Eventually this cooperation will come, for it is becoming increasingly more essential now for the doctor to interest himself in problems of heredity. The result of modern methods of hygiene and treatment has been to protect and preserve to a fertile age many individuals who years ago would have succumbed before this period was reached. Such contraselective characteristics of our civilization now tend "to preserve and accumulate abnormal mutations, whether visible defects or hidden physiological peculiarities."[31] A good example of this is seen in diabetes which is recognized as an inheritable disease. Successful palliation of this disorder has permitted more diabetics to reach the child-bearing age and has transformed the diabetic woman into a fertile rather than a relatively sterile individual. Furthermore,

it has resulted in a considerable reduction in both the maternal and fetal mortality rates of this group. Other examples of this nature point to the fact that in the future the increasing incidence of inheritable disease will of necessity create more interest in the racial and eugenic aspects of preventive medicine. Hence, the physician will be required to give more advice or information regarding the probability of a given trait being transmitted to the child, that is, a eugenic prognosis. This cannot be accomplished unless the medical curriculum is modified to include courses in genetics. These should be organized to supply the student with a working knowledge of genetics which will be applicable to clinical medicine.

In undertaking to ascertain the inheritance element in disease it will be found that this can be detected with striking clarity in some cases while in others it is more obscure and nebulous. There are well-known reasons for this. Man is a poor breeder and a slowly maturing animal so that the turnover of generations is only about three to the century. Pure strains are practically nonexistent owing to outbreeding, and experimental breeding is impossible. Family pedigrees are difficult to trace and are usually too meager to be of value in genetic analyses. One of the outstanding difficulties in tracing pedigrees is failure to realize that recessive traits may not be visible in several generations. Morgan[46] considers it rather hazardous to attempt to apply even the simpler rules of mendelian inheritance to man because of his complex genetic composition. The development of many inherited human characteristics depends to a large extent on the presence of modifying factors and on external environment for their expression. Such a complexity makes him disrespect the human as genetical material and question the simplicity with which some write of complicated processes of human inheritance.[47] Thus, one would infer that the physician in his admission of ignorance about human heredity is joined by only a few of his geneticist colleagues. The medical man has come in for no little criticism and ridicule by students of heredity because of his lack of genetic technic in dealing with an acknowledged complex problem in an animal that can neither be experimented with nor compared satisfactorily with others. Of necessity more devious routes must be taken to secure information of a sort that may be of a little value to the human race. For this reason some of the so-called archaic but "well-intended" efforts of the medical profession to classify man into gross physical types, constitutions, or diatheses, must be continued even though they are considered "so far in advance of our genetical information that the geneticist may be excused if he refuses to discuss them seriously."[46] If for nothing but humanitarian reasons, and after all medicine is not a cold mathematical science, these constitutional types which have been fostered by the continental writers[48] will continue to be used as diagnostic and prognostic aids until something more constructive is offered. In other words, groupings of this sort, which have existed in some form for centuries, have served the physician good stead and will be used by him until the geneticist can apply his experimental and biometric methods to human material. To some extent this method of approach is now being tried in some of the biologic institutes of Russia and Germany.[49] Robb,[50] in perusing medical literature, finds that the medical author does not give due credit to the recessive genes in etiology and decrys the use of the "ubiquitous label 'familial but not hereditary'" which has been used to convey the fact that the parents apparently show

none of the abnormal traits exhibited by the offspring. He also notes that lethal and semilethal factors are rarely identified although the latter were responsible for 13 per cent of infant deaths in 1929 as compared with 1.5 per cent 40 years ago. These figures emphasize the increasing importance of the eugenic prognosis in medicine. The behavior of allelomorphs, likewise, does not seem to have been generally appreciated in medical writings. Criticisms of this nature should stimulate the medical profession to greater interest in genetics so that the little that has been found out about the human can be utilized to the fullest extent. So far, it does not seem to the reviewer that medical men in general have appreciated sufficiently the use that studies of twins can be put to in the evaluation of human heredity.

It has been observed, as mentioned above, that certain structural and physiologic characteristics are peculiar to the members of certain families.[51] Such traits or predispositions to them are primarily of a hereditary nature but are subject to environmental influences to an extent that at times they will tend to appear only when these environmental conditions are present. In order to correlate the numerous but confusing observations relative to this subject, an attempt has been made by some to classify roughly these gross physical states or types so that a better perspective may be had of man's tendency to react along certain clinicopathologic lines. This system of grouping has been of considerable value to the clinician in many ways, especially in respect to diagnosis, prognosis, and prophylaxis. Thus, it has helped the doctor to recognize disease in the making. It has made it easier for him to try to anticipate and forestall disease by entering, gropingly to be sure, a sort of prepathologic realm where minor variations or incipiencies develop into the potential and finally the recognizable disease state. In this way it gives him, at least, an opportunity to attempt to follow out the principle that the best treatment is prevention. Thus, the intimation that certain types of individuals react somewhat typically to certain environmental influences gives the physician a chance to be on the lookout for disease at a time when it can be more successfully treated or prevented. This grouping of individuals has helped to correlate much scattered information so that a better composite picture, for instance, of metabolic and hormonic disturbances, could be painted. It has been through this method that the subtle influence of the endocrines upon the individual has been brought out. It must be realized that this particular phase of medicine is merely a makeshift used to bridge over tremendous gaps in our knowledge. For this reason, there is little need to create an extensive and detailed classification as it would make the subject too complicated and really a comprehensive study of syndromes. At present the pediatrist can continue to utilize successfully in his practice some of the information gained by reading of the so-called archaic diatheses which have been included in pediatric texts for years: exudative, lymphatic, neuroarthritic, and spasmophilic. While the diathetic concept is beyond the pale of scientific preciseness demanded by pathologist and geneticist, for the clinician it still serves a definite purpose. The diatheses, or constitutions, should be considered as merely impressions based upon astute clinical observations which serve to assist the clinician temporarily until these impressions can be metamorphosed into biologic facts.

In the past few years geneticists have furnished physicians with abridged information about human inheritance. This has been of value

in helping them to give more satisfactory eugenic prognoses and in interesting them in the accumulation of hereditary pedigrees. Several monographs worthy of reading have been published, most of which include interesting data about the more common diseases in man which seem to show fairly well-proved transmissibility. It must be remembered, however, that, while heredity may be demonstrated in a given disease, other factors should not be ignored. In fact, as has been emphasized before, heredity and environment must be considered inseparable, and the concept of the gene must include three components: the gene matter, situated in the chromosome; the relation to other genes, the genetic environment; and the external environment.[52] In giving genetic advice, "judgment should always be given with the reservation involved in the fact that genetics primarily deal with *probabilities*" [italics ours].[53]

Briefly the present-day conception of genetics is that the chromosomes form the basis of the mechanism of inheritance. They carry within themselves the genetic factors known as genes, which are likened to a string of beads the individual members of which represent the character determinants. Genes are relatively stable but on rare occasions may change, thus causing mutations. These factors usually work in conjunction with one another. When chromosomes subdivide, they split longitudinally so that the line of genes is split likewise, each daughter chromosome receiving exactly half of the original line. All characters are in pairs called allelomorphs (alternates) one of which is usually dominant and the other recessive. Thus, while the dominant characteristic may be the only one apparent in the individual, a recessive factor may be present. A recessive gene may be transmitted for generations before it meets a similar gene in another individual and the recessive character becomes visible. This process makes it difficult to trace heredity in humans. If an individual inherits the same gene from both his parents he is homozygous, or pure for that character. If he inherits a dominant and a recessive gene, then he is in a hybrid or heterozygous condition. In the inheritance of dominant characteristics the character appears in every generation. Some genes are dominant to one and recessive to another so that irregularity of reaction may appear. Homozygous dominants are rarely found. Heterozygous dominants usually marry normals so that half of the children will be of each type. When a heterozygous dominant marries a recessive, about half of the children will be of the recessive type. When two heterozygous dominants cross, about one-fourth of the children will be of the recessive type. In the human race, families are often so small that these ratios may not appear. The pedigree of recessive inheritance is different. It may be transmitted for generations before it meets the same gene in another individual. This is the danger in cousin marriages. Inbreeding accumulates recessive defects as well as dominant defects whether they be good or bad. When the genes are carried in the sex chromosomes they are said to be sex-linked. In such instances the characteristic is usually carried by the female and manifested in the male. Lethal factors, or genes, may prevent the development of the gamete or zygote by causing intrauterine death, which may occur early or late. Semilethal factors are likely to cause postnatal death. Lethal factors are recessive, appearing only when present in a homozygous condition.

Fertility.[54]—There is a significant correlation between the number of children born to women and to their mothers. Therefore, the heredity of fertility seems to be established.

Multiple Births.[55, 56-68]—The ratio between twins and single births is 1:85 and between triplets and single births 1:87.[2] Triplets occur once in 7,000 births. Heredity factors are of importance in twinning, both parents transmitting the tendency. It is recessive. Multiple births are more often girls than boys. Repetition of twins occurs about once in twenty times. Approximately 15 per cent of all women have the twinning tendency, so that in a given pregnancy the chance that one of these women will actually produce twins is 1:10.

Physical Characteristics.[57, 58]—Stature seems to be related to heredity. In tall families the normal offspring are characteristically tall, and in short families the reverse holds true. A slight regression may appear in the younger generations in tall families, but in short ones there is no increase. Thus, shortness seems to be due to positive or dominant factors that limit growth while the factors for tallness are probably recessive. Brown eye color is incompletely dominant to blue, several genes probably being involved. Blue eye color is recessive to brown but dominant to red (albinism). In general, the darker hair colors appear to be dominant over the lighter colors, as with skin colors. Red hair is apparently recessive.

Skin.—*Psoriasis* shows a definite hereditary character in a large number of cases. The common mode of inheritance is probably recessive, and, therefore, no more than one-fourth the children will be affected. Skipping of a generation is often observed. *Ichthyosis* is a variable inheritable trait conforming to several forms of inheritance. *Nevi* adhere chiefly to the dominant type, especially when on the cheek. *Albinism* is usually transmitted as a mendelian recessive trait. It has been estimated that in random mating there would be about one person in seventy carrying the gene for albinism. *Pattern baldness* is inherited from father to son as a dominant. When the woman transmits, it acts as a recessive. The condition is usually sex-limited. The pattern is usually constant in families and frequently the pattern can be outlined in the newborn.

Skeleton.—The *teeth* are subject to a number of inherited anomalies, the most common one being the absence of one or more. It appears to be both dominant and recessive. Studies of identical twins suggest that early decay may have sometimes a background of inheritance as does the time and order of their appearance of teeth. *Osteogenesis imperfecta* behaves as a mendelian dominant as probably does *achondroplasia* and *dysostosis cleidocranialis*. In such cases parenthood is inadvisable. *Cleft palate and cleft lip* shows an inheritable recessive tendency at times, but in many pedigrees it seems to be purely sporadic and accidental. The same may be said for *congenital dislocation of the hip*. *Clubfoot* in about one-half of the cases seems to have a hereditary background requiring a guarded prognosis as to the probabilities of the defect in the offspring. Eleven per cent of the offspring of normal persons mated with affected ones are found to be affected. *Flatfoot* is also reported to be largely inherited. *Polydactylism, syndactylism, and brachydactylism*[59-62] can occur in normal families as sporadic sports, but the group shows a striking hereditary character which usually acts as a dominant. A guarded eugenic prognosis must be given.

Eye.—Knowledge of the hereditary transmission of ocular defects is unusually complete. *Refractive errors* manifest a hereditary tendency of a complicated type owing to the interplay of several factors. In the normal emmetrophic condition hereditary transmission seems to be domi-

nant. *Myopia* frequently appears as a recessive or dominant character, and occasionally its transmission may be sex-linked. Consanguinity in parentage, therefore, definitely affects the incidence of myopia. It is the only refractive error serious enough in its implications to warrant attempts to limit its incidence in future generations. While abuse of the eyes plays a part, it cannot be considered the primary cause of the disorder. *Hypermetropia* of the milder type is dominant in character, while the high-grade type which is sometimes associated with cataract is usually recessive in character. *Astigmatism* is frequently an inherited error and like smaller errors of refraction is usually transmitted as a dominant. *Squint* shows inherited tendencies, but there seems to be no constancy about its behavior. *Retinitis pigmentosa* is definitely hereditary and, although acting as a dominant in most cases, may appear as a recessive occasionally. Transmission of other hereditary diseases of the retina is usually of a recessive nature. *Amaurotic family idiocy* seems to be transmitted as a recessive character and *congenital optic atrophy* as a dominant. *Congenital night blindness* may be inherited as either a dominant or recessive and in some instances it is sex-linked. *Color blindness* of the red-green type, which shows an incidence of 8 per cent in males and 0.5 per cent in females, is usually inherited as a typical male sex-linked character. It is recessive in the female. The rarer form, total color blindness, is transmitted as a recessive character. *Congenital cataract* is strongly hereditary being transmitted as a dominant character. Since 13 per cent of the inmates of blind schools have the disease, eugenic measures should be used to combat its production. *Infantile glaucoma (buphthalmos)* behaves as a recessive. *Congenital nystagmus* and *congenital ptosis* are usually found to be transmitted as dominant characters. Sex-linking may occur in the former.

Ear.—Deaf-mutism is inherited in about one-seventh of the cases as a mendelian recessive factor. It is more likely to appear in consanguineous marriages. When both parents are deaf-mutes, conception should be interdicted. If one parent suffers from the defect, and the other is normal and has a normal pedigree, the chance of deaf offspring is small although a few of these will be recessive to hereditary deaf-mutism. However, if the normal parent has a family history of deaf-mutism, about as high as 35 per cent of the resulting families will contain deaf-mutes. If both parents have normal hearing but come from a family with a tendency to the disease, the chance for deaf children is so high that conception should be prevented. *Otosclerosis* occurs frequently enough, one in two hundred, to engage the interest of many prospective parents. The disease is more common among females. There is a hereditary basis for the disease, but no uniform manner of transmission is found. When both parents come from affected stocks, the prospect for the children is bad. There is slightly less likelihood for otosclerosis in the offspring when the husband is deaf and his pedigree shows the disease than when the same situation prevails in the wife. When either parent is affected but the pedigrees of both are normal, the risk is less. It is often difficult to differentiate between otosclerosis and adventitious deafness in the pedigree.

Blood.—Blood groups are distinctly subject to heredity, but, owing to a peculiar condition known as multiple allelomorphism, hereditary transmission of these groups is not generally understood. In this in-

stance the original recessive gene, which may be designated "O," is thought to have given rise to two dominant genes A and B. The groups are represented in the following way:[56]

Group	Genes
I	OO
II	AA or BO
III	BB or BO
IV	AB

Since both A and B are dominant to O either AA or AO will act alike and result in Group II. The same can be said for BB and BO in Group III. From this it is possible to understand why union between parents of blood Groups I and IV will result in offspring whose blood characteristics will not resemble that of either parent. The children's bloods will conform to either Group II or III. Such knowledge is of inestimable value in seeking donors because it may make it possible to eliminate many obviously unnecessary tests for compatibility. Diseases of the blood have been found to manifest striking inherited tendencies. *Hemophilia* is a sex-limited disorder which is transmitted only by females and manifested by males. With a carrier mother and a normal father 50 per cent of the sons will be affected, all the daughters should be normal, but 50 per cent should be carriers. With a normal mother and an affected father all the siblings should be normal, but all the daughters, carriers. It would be expected that one in 200 females should manifest the disease. Actually few if any do. This may be due to a lethal factor which kills the offspring *in utero*. From a eugenic standpoint only the unaffected males of a hemophilic family should be permitted to propagate. *Acholuric jaundice* or familial hemolytic anemia is inherited as a mendelian dominant as is *sickle-cell anemia*. There are a number of blood diseases which afflict several members of a family but about which there is an insufficient amount of authentic information regarding its transmissibility through successive generations. In this group belong familial icterus of the newborn, erythroblastosis, Gaucher's disease, and lipoid histiocytosis.

Nervous System.—Migraine is considered to be transmitted as a mendelian dominant, but, since the presence of exogenous factors play an important part in its production, inheritance studies are difficult to make. Apparently, even though a dominant, it can be transmitted by individuals who do not suffer the disease. *Huntington's chorea* is, likewise, inherited as a mendelian dominant. Nearly all the cases in the United States have been traced to three brothers who emigrated to this country in the seventeenth century.[62] Its behavior is that of a typical mendelian dominant uninfluenced by sex. It is clear that patients with the disease should not marry. Although *paralysis agitans* is usually sporadic, it may appear as either a dominant or recessive character. *Amaurotic family idiocy* is a vicious disorder showing evidence of being transmitted as a mendelian recessive. The genes are sublethal. It may also be classed as one of the abiotrophies. Brain[21] uses the term *hereditary ataxia* for a group of disorders having more or less common clinical features; *Friederick's ataxia* and *Marie's cerebellar ataxia* are the most common forms. The former usually operates as a simple dominant or recessive, but sometimes a more complicated inheritance seems to be present. Affected members may transmit the disorder

to as high as 30 per cent of their offspring and apparently unaffected members, to 13 per cent. Children of affected parents are more likely to suffer the disease than those remotely related to an affected individual. *Peroneal muscular atrophy* may be transmitted as either a dominant or recessive which may be sex-linked. The *muscular dystrophies* seem to act in the same variable way and eugenic prognoses must not be made until the individual has passed the age at which symptoms usually appear in members of the family. In *myotonia congenita* inheritance seems to be a dominant. *Neurofibromatosis* appears to be inherited as a mendelian dominant, and, therefore, those free from the disease will not transmit it. *Spina bifida* is often inherited as a dominant trait. *Epilepsy*[60] may or may not be an inherited disease in about 50 per cent of the cases. Owing to the fact that, when the predisposition is present, it may take an additional factor such as an acquired cerebral lesion to initiate the symptoms, it is impossible to trace accurately the heredity of the disease. Multiple heritable factors rather than simple ones are probably present. The chances are about 1 to 10 that an epileptic will transmit the disease to its offspring, and transmission seems to be equal in both sexes. In the case of the *petit mal* form, the risk of inheritance is somewhat less.

In respect to the inheritance of mental disorders, there have been so many inadequately controlled studies, histories are so difficult to obtain, and the material itself is subject to such a great number of variable factors that positive statements about it are practically impossible to make. In general, it may be said that such disorders as schizophrenia and manic-depressive insanity are transmitted, and there is no reason to change the eugenic prognosis if these disorders have been recovered from. There is reason to believe that criminals, moral defectives, impulsive hysterics, severe hypochondriacs, obsessionals, and alcoholics are probably unsuitable progenitors.[31] Definite mental defectives are likewise unsuitable progenitors, and, when familial taints are present in both parents, transmission is likely. When there is a family history of mental deficiency on one side and of soundness on the other, transmission to the immediate offspring is not so likely. *Mongolism* is probably not transmissible. However, as has been mentioned before,[45] there is a greater chance for some form of malformation in subsequent children when a woman has produced one child with a gross abnormality. Further childbearing after the age of thirty-five in such women should not be encouraged.

Metabolic Disturbances.—Diabetes mellitus[64] shows definite hereditary tendencies in at least 25 per cent of the cases, but the mode of transmission is not sufficiently clear to state exactly the mendelian principle involved. Several genes may be involved. When there are numerous diabetics in the pedigree, there is a probability of transmission, and, if both sides are involved or the disease is present in every generation, dominance of the trait is suggested, and the chances of transmission are strong. The chances for a diabetic to beget an offspring with the tendency is high. With the modern method of treating diabetics the disease is not incompatible with subsequent economic efficiency. Since the fertility of the treated diabetic has been greatly increased and since the lethality of the disease from both the maternal and fetal standpoint has been substantially decreased, we are now faced with an increased incidence of diabetes in our population.[65] *Renal diabetes* appears to behave as a dominant character and such rare

disorders as alkaptonuria, cystinuria, pentosuria, porphyrinuria, and steatorrhea are thought to be recessives.

Allergic Diseases.—There is rather definite evidence that the allergic tendency may be transmitted. However, since the incidence of the disturbance in families surpasses the expected proportions for mendelian inheritance, undoubtedly in many cases it is an acquired abnormality. Placental transmission has been reported.[66] It is thought, however, that inheritance can be explained in the majority of cases on the basis of mendelian dominance.[67] In 50 per cent of affected individuals the pedigrees will show the trait on one side, and in 20 per cent it will be found on both sides. In angioneurotic edema there seems to be a clear-cut dominance.

LETHAL FACTORS

While there is every reason to expect that lethal factors exist in man as well as animals and plants, direct evidence to substantiate this belief is difficult to obtain. Some but not all the monstrosities appearing at birth are probably of this origin, and perhaps some miscarriages are due to the action of lethal genes. Congenital ichthyosis seems to be a good example of a lethal factor at work. Sublethal genes are thought at times to be involved in the following conditions: xeroderma pigmentosa, osteogenesis imperfecta, glioma retinae, spinal progressive muscular paralysis, amaurotic family idiocy, spina bifida, hydrocephalus, cretinism, and mongolism. Unfortunately some of these are too viable in man. Since lethal factors exist only in the recessive state, except possibly for brachydactyly, it is very hard to get accurate information about them. As Mohr states, it is surprising that there is such a perfect coordination between the numerous genes that embryologic abnormalities are relatively infrequent.

From the foregoing brief résumé it can be seen that the present-day knowledge about human inheritance is meager and most unsatisfactory. This is due to the complexity of man's genetic make-up as well as to the difficulty in obtaining reliable pedigrees. In order to satisfy the statistical laws upon which genetics are based, it is necessary to deal in large numbers. Single pedigrees rarely do this. Furthermore, the data from pedigrees extending over many generations is unreliable not only because hearsay evidence must be relied on for the earlier generations, but also because diagnoses and diagnostic methods change. Pooled data from two-generation pedigrees, therefore, are much more reliable scientifically than data from a few pedigrees of many generations. The medical profession can be of infinite service in obtaining pedigrees for these pools, provided it learns how to take them properly. Pedigree blanks may be obtained from the Eugenics Record Office.

The method of dealing with the problem of heredity in the human differs from that in animals or plants. It is not possible to build a race free from defects, nor is it always desirable. For instance, it is better to eradicate an infectious disease by such public health measures as sanitation and individual immunization, e.g., typhoid, than to try to breed a race immune to the disease. Consanguineous marriages or inbreeding among tainted families as a means of localizing the disorder does not seem to be justifiable or possible. So far, sterilization of defectives has not met with much popular success. Such problems belong rather to the sociologist and the eugenist than the doctor. The little that can be accomplished, at present, must come through efforts to discourage procreation among hereditary defectives.

From a medical standpoint the greatest attention should be focused upon removing the external causes of disease and protecting against disease.

SUMMARY

1. Present-day lack of uniformity in definitions and bases for statistical analyses tends to prevent accumulation of accurate information about the underlying causes of fetal and neonatal deaths.

2. In an attempt to overcome such difficulties, an outline and group of definitions agreed upon by several organizations interested in the subject is herewith presented.

3. Some of the possible etiologic factors in the production of congenital defects are reviewed.

4. The brief résumé of the present status of human inheritance presented emphasizes the meagerness of our information about this complex subject.

5. The medical profession is urged to take greater interest in human genetics in order that more authentic information may be made available to geneticists and more satisfactory eugenic prognoses may be given to prospective parents.

REFERENCES

1. Bonar, B. E.: Problems of the Newborn, J. PEDIAT. 5: 216, 1934.
2. Bonar, B. E.: The Newborn, J. PEDIAT. 7: 99, 1935.
3. Grier, R. M.: Fetal Mortality, Am. J. Obst. & Gynec. 22: 890, 1931.
4. Taussig, F. J.: Abortion and Its Relation to Maternal Mortality. To be published.
5. Pfaundler, M.: The Diseases of Children, Pfaundler and Schlossmann. English translation. Vol. 1, p. 34, Philadelphia, 1935, J. B. Lippincott Company.
6. Young, J.: Maternal Mortality and Maternal Mortality Rates, Am. J. Obst. & Gynec. 31: 198, 1936.
7. Clifford, H.: A Study of Neonatal Mortality, J. PEDIAT. 8: 367, 1936.
8. Special Report: Stillbirths, Am. Pub. Health A. Yearbook, 1935-36.
9. Manual of International Causes of Death, 1924, p. 379.
10. Feldman, W. M.: The Principles of Antenatal and Postnatal Child Psychology, New York, 1920, Longmans, Green & Company, p. 142.
11. Scammon, R. E.: Abt's Pediatrics 1: 353, 1923, Philadelphia, W. B. Saunders Company.
12. Hess, J. H.: Premature and Congenitally Diseased Infants, Philadelphia and New York, 1922, Lea & Febiger, p. 364.
13. Hess, J. H., Mohr, G. J., and Bartelme, P. F.: The Physical and Mental Growth of Prematurely Born Children, Chicago, 1934, The University of Chicago Press, p. 221.
14. Swanson, W. W., Turner, A. R., and Adair, F. L.: Institutional Mortality of the Newborn, J. PEDIAT. 7: 516, 1935.
15. Streeter, G. L.: Focal Deficiencies in Fetal Tissues and Their Relation to Intrauterine Amputation, Pub. No. 414, 1930, Carnegie Institute, Washington, D. C.
16. Musselmann, L. K.: Natural Immunity of the Newborn, Am. J. Obst. & Gynec. 8: 45 and 141, 1924.
17. McKahnn, C. F., and Chu, F. T.: J. Infect. Dis. 52: 268, 1923; and Tr. Am. Pediat. Soc. 45: 65, 1933.
18. McCarty, V. W.: Otological Observations in the Congenitally Syphilitic Child, Tr. Am. Laryng. Rhin. & Otol. Soc. 38: 479, 1932.
19. Cruickshank, J. N.: The Causes of Neonatal Death, M. Research Council. Special Report Ser. 145, London, 1930, H. M. Stationery Office.
20. Peckham, C. H.: Fetal Mortality in the Toxemias of Pregnancy, J. A. M. A. 101: 1608, 1933.
21. Ronsheim, J.: Diabetes and Pregnancy, Am. J. Obst. & Gynec. 25: 710, 1933.
22. Campbell, A. M.: The Effect of Excessive Cigarette Smoking on Maternal Health, Am. J. Obst. & Gynec. 31: 502, 1936.
23. Sontag, L. W., and Wallace, R. F.: The Effect of Cigarette Smoking During Pregnancy on the Fetal Heart Rate, Am. J. Obst. & Gynec. 29: 77, 1935.

24. Sadler, E. S., Dilling, W. J., and Gemmell, A. A.: Further Investigations Into the Death of the Child Following the Induction of Labor by Means of Quinine, J. Obst. & Gynaec. Brit. Emp. 37: 529, 1930.
25. Torland, T.: Fetal Mortality After Induction of Labor by Castor Oil and Quinine, J. A. M. A. 10: 1190, 1928.
26. King, E. L.: Does Quinine in the Induction of Labor Have a Deleterious Effect on the Fetus? J. A. M. A. 101: 1145, 1935.
27. Taylor, H. M.: Prenatal Medication as a Possible Etiologic Factor in Deafness of the New Born, Arch. Otolaryng. 20: 790, 1934.
28. Taylor, H. M.: Further Observations on Prenatal Medication as a Possible Etiologic Factor of Deafness in the Newborn, South. M. J. 28: 125, 1935.
29. Pearl, R.: The Effect of Parental Alcoholism and Certain Other Drug Intoxications Upon the Progeny, J. Exper. Zool. 22: 573, 1917.
30. Durham, F. M., and Woods, H. M.: Alcohol and Inheritance, M. Research Council, Special Report No. 168, 1932.
31. Blacker, C. P.: The Chances of Morbid Inheritance, Baltimore, 1934, William Wood & Company, p. 152.
32. Schmucker, S. C.: Heredity and Parenthood, New York, 1929, Macmillan Company, p. 118.
33. Bagg, H. J.: Hereditary Abnormalities of the Limbs, Their Origin and Transmission, Am. J. Anat. 43: 167, 1929.
34. Fitchet, S. M.: The Etiology of Congenital Hereditary Deformities, New England J. Med. 213: 164, 1935.
35. Miller, J. R., Corscaden, J. A., and Harrar, J. A.: The Effects of Radiation on the Human Offspring, Am. J. Obst. & Gynec. 31: 519, 1936.
36. Findlay, P.: Pelvic Irradiation in the Child-Bearing Woman, J. A. M. A. 95: 857, 1930.
37. Jansen, M.: Feebleness of Growth and Congenital Dwarfism, 1921, Oxford University Press.
38. Peterson, W. F.: The Distribution of Congenital Malformations in the United States, Am. J. Obst. & Gynec. 28: 70, 1934.
39. Peterson, W. F.: The Seasonal Trend in the Conception of Malformations, Ibid. 28: 445, 1934.
40. Stockard, C. R.: Developmental Rate and Structural Expression, Am. J. Anat. 28: 115, 1921.
41. Murphy, D. P.: The Month of Conception for 935 Malformed Individuals, Am. J. Obst. & Gynec. 31: 106, 1936.
42. Murphy, D. P.: Maternal Age at Conception of the Congenitally Malformed Child, Am. J. Dis. Child. 51: 1107, 1936.
43. Murphy, D. P., and Maser, M.: The Birth Order of Five Hundred and Eighty-Two Malformed Individuals, J. A. M. A. 105: 849, 1935.
44. Graves, G. W.: The Consideration of Genetic and Developmental Factors From the Pediatrist's Viewpoint, Arch. Pediat. 52: 649, 1935.
45. Murphy, D. P.: Congenital Defects, J. A. M. A. 106: 457, 1936.
46. Morgan, T. H.: The Relation of Genetics to Physiology and Medicine, Scientific Monthly 41: 5, 1935.
47. Morgan, T. H.: The Scientific Basis of Evolution, New York, 1932, W. W. Norton & Company, Inc.
48. Pende, N.: Constitutional Inadequacies, English Translation, Philadelphia, 1928, Lea & Febiger.
49. Muller, H. J.: Human Genetics in Russia, J. Hered. 26: 193, 1935.
50. Robb, R. C.: Discrepancies of Etiology in Ten Medical Text Books Now Used at Syracuse University, J. A. Am. M. Coll. 10: 295, 1935.
51. Draper, George: The Human Constitution, Philadelphia, 1924.
52. Hogben, L.: Nature and Nurture, New York, 1935, W. W. Norton & Company, Inc.
53. Mohr, O.: Heredity and Disease, New York, 1934, W. W. Norton & Company, Inc.
54. Fisher, R. A.: The Genetical Theory of Natural Selection, 1930, Oxford Press.
55. Brown, M. J.: Twinning in the Hebard Family, J. Hered. 26: 115, 1935.
56. Popenoe, P.: The Child's Heredity, Baltimore, 1929, Williams & Wilkins Company.
57. Davenport, C. R.: Inheritance of Stature, Genetics 1: 313, 1917.
58. Fantham, H. B., and Porter, A.: Inheritance of Stature Through Selection, J. Hered. 26: 377, 1935.
59. Branders, J. W.: Polydactylism as a Hereditary Character, J. A. M. A. 64: 1640, 1915.

60. Murphy, D. P.: Five Successive Generations of Webbed Finger Deformity, J. A. M. A. 84: 576, 1925.
61. Snyder, L. H.: Recessive Factor of Polydactylism in Man, J. Hered. 20: 73, 1929.
62. McClintic, B. S.: Five Generations of Polydactylism, J. Hered. 26: 141, 1935.
63. Davenport, C. B., and Weeks, D. F.: J. Nerv. & Ment. Dis. 38: 64, 1911.
64. Macklin, M. T.: Inherited Anomalies of Metabolism, J. Hered. 24: 349, 1033; and 25: 123, 1934.
65. Skipper, E.: Diabetes Mellitus and Pregnancy, Quart. J. Med. 2: 353, 1933.
66. Kuttner, A., and Ratner, B.: The Importance of Colostrum to the New Born Infant, Am. J. Dis. Child. 25: 414, 1923.
67. Smith, J. J., et al.: Occurrence of Hypersensitiveness or Allergy in Five Generations of One Family, Arch. Int. Med. 41: 472, 1928.
68. Davenport, C. B.: A Strain Producing Multiple Births, J. Hered. 10: 382, 1919.
69. Brain, W. R.: The Inheritance of Epilepsy, Quart. J. Med. 19: 299, 1926.

The following works have been consulted in the preparation of this review:

Abt, I.: Abt's Pediatrics, Vols. 1 and 2, Philadelphia, 1926, W. B. Saunders Company.
Blacker, C. P.: The Chances of Morbid Inheritance, Baltimore, 1934, William Wood & Company.
Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, 1933, Oxford University Press.
Fisher, R. A.: The Genetical Theory of Natural Selection, 1930, Oxford University Press.
Hogben, L.: Nature and Nurture, New York, 1933, W. W. Norton & Company, Inc.
Mohr, O. L.: Heredity and Disease, New York, 1934, W. W. Norton & Company, Inc.
Morgan, T. H.: The Scientific Basis of Evolution, New York, 1932, W. W. Norton & Company, Inc.
Morgan, T. H.: The Theory of the Genes, New Haven, 1928, Yale University Press.
Pfaundler, M., and Schlossmann, A.: The Diseases of Children, English Translation, Peterman, Vols. 1 and 2, Philadelphia, 1935, J. B. Lippincott Company.
Popenoe, P.: The Child's Heredity, Baltimore, 1929, Williams & Wilkins Company.

9 Exchange Place

American Academy of Pediatrics

Proceedings

SIXTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

KANSAS CITY, MAY 11 AND 12, 1936

Round Table Discussion on Prophylaxis and Treatment of Whooping Cough

Chairman: Dr. E. J. Huenekens, Minneapolis, Minn.

Assistants: Dr. W. L. Bradford, Rochester, N. Y.; Dr. J. M. Frawley, San Francisco, Calif.; and Dr. Louis W. Sauer, Evanston, Ill.

CHAIRMAN HUENEKENS.—This is the third successive year that pertussis has been a subject for round table discussion. The prophylaxis and the treatment of pertussis are decidedly live subjects and also it is difficult to arrive at satisfactory conclusion as to the value of the various measures prepared for its control, for the test of treatment both prophylactically and therapeutically must be judged largely on an empirical basis. Some of the questions we propose to discuss today are: (1) Can we produce active immunity against pertussis? (2) If so, how long does it persist? (3) Which vaccine, Madsen's, Sauer's, or Krueger's, is most effective? (4) What methods, other than vaccines, are available? (5) Are vaccines effective in treatment? Obviously, we cannot give the final answers to these questions today, but we can report progress.

While there can be no doubt that preventing whooping cough is more important than subduing it after it has occurred, nevertheless we must not permit our enthusiasm for prophylaxis to blind us to the need of considering treatment.

I think that vaccine administered during the incubation period of the disease, or even during the early catarrhal stage, is of some therapeutic value. Madsen, of Copenhagen, says: "Most of the reports conclude that if given early in the catarrhal stage, the vaccine will have a good effect. This appears from the reports of most of the Danish officers of health, and also is the consensus of the Danish Pediatric Society." It must be conceded that judgment on the therapeutic value of the vaccine does not lend itself to statistical analysis. Statistics are only of value when a catagorical answer of yes or no can be given. When the answer must be given in degrees of improvement, statistics have relatively slight value. But even though the value of therapeutic effectiveness of vaccine is difficult to gauge, it does not follow that we can lightly dismiss it. The discussion in last year's round table conference encouraged the distinction that Sauer's vaccine is especially adopted for prophylaxis, while Krueger's vaccine is more effective for therapy. It would seem that the vaccine which is finally judged to be more effective in prophylaxis should also be better therapeutically and vice versa. A frank discussion of this subject would be a distinct contribution.

Another point which might be profitably considered is the contention that, during the four-month period while the child is developing his active immunity to pertussis,

no other immunizations should be administered. One could imagine that a severe case of measles or scarlet fever with high fever and prostration might interfere with production of immunity by pertussis vaccine. But that the slow nonincapacitating immunization by diphtheria toxoid or pertussis vaccine should interfere with each other is rather a strain on our credulity.

These and any similar questions pertaining to the prophylaxis and treatment of pertussis should be discussed frankly here today.

I had asked Dr. Pearl Kendrick, Associate Director and Bacteriologist of the Michigan Department of Health, to assist in this round table discussion, but she is unable to be present. However, she has kindly permitted me to present the latest reports on her work here today.

"Since the latter part of 1932, a study of whooping cough has been in progress in Grand Rapids. The work has been outlined and certain bacteriological findings have been summarized in previous reports. In this paper we are reporting our findings to date in connection with our investigation of the value of *B. pertussis* vaccine in the prevention of whooping cough. Our study has not been carried on for a sufficient time nor do our results embrace sufficient numbers to warrant final conclusions. However, we believe they do contain sufficient of interest to justify a progress report.

"The vaccine used has been described.* Briefly, it is a once-washed 10,000 million per cubic centimeter suspension of *B. pertussis*, Phase 1 of Leslie and Gardner, grown on Bordet-Gengou medium enriched with 15 per cent sheep's blood. The organisms are killed with merthiolate 1:10,000 or phenol 0.5 per cent allowed to act at cold-room temperature for a week or more.

"The optimum dosage by no means has been determined. Sauer used more than three times as large a total dose of vaccine as Madsen—perhaps the most important difference between the procedures of these two authors. The fact that Sauer reports such excellent protection results calls attention to the need for considering the question of total amount of injected antigen. In most of our vaccine-treated individuals we have used a total quantity of vaccine close to that suggested by Sauer."

WHOOPING COUGH PREVENTION STUDY*

TOTAL IN STUDY APRIL 15, 1936—2,285

EXPOSURES AND CASES IN STUDY SERIES TO DATE, APRIL 15, 1936

KIND OF EXPOSURE HISTORY	VACCINE-INJECTED GROUP			CONTROL GROUP			TOTALS		
	EXPOSED	CASES		EXPOSED	CASES		EXPOSED	CASES	
		NUMBER	% OF EXPOSED		NUMBER	% OF EXPOSED		NUMBER	% OF EXPOSED
Definite	60	9	15.0	72	58	80.5	132	67	50.75
Indefinite	55	3	5.5	51	27	52.9	106	30	28.30
None	3	3	----	26	26	----	29	29	----
Totals	118	15	12.7	149	111	74.5	267	126	47.2
Per cent of total cases		11.9			88.1			100.0	

*From the Michigan Department of Health, Bureau of Laboratories, Western Michigan Division, Grand Rapids.

The Use of Immune Blood in Whooping Cough and Its Effect Upon Phagocytosis

W. L. Bradford, M.D.

Although recent evidence does not support a filtrable virus as the sole cause of whooping cough, further investigation to determine the value of immune blood as a prophylaxis for the exposed baby is justified. The reasons for this attitude

*Kendrick, Pearl, and Eldering, Grace: Progress Report in Pertussis Immunization, Am. J. Pub. Health, 26: 8, 1936.

are: (1) The immunizing power of vaccine in the very young infant is not yet known. (2) It is probable that very young infants do not respond favorably to antigenic stimulation. (3) In the exposed infant, the time interval may not permit proper active immunization. (4) There is evidence that immune serum neutralizes the skin-necrotizing substance of *H. pertussis* and to a certain extent protects animals against lethal dosages of virulent organisms.

Since 1931 we have been interested in the administration of immune adult blood and of convalescent serum to babies obliged to remain in family contact with cases of whooping cough.

During the interval from June 1, 1931, to Sept. 1, 1934, forty-four such infants were given this type of prophylaxis. The results, along with a review of the literature, were recently published.[1] In general, it seemed probable that immune blood was effective in the prevention and modification of the disease when given before the catarrhal symptoms appeared.

Since 1934, about twenty-five additional infants have been similarly treated. The results obtained in this second group were similar to those observed previously in the first group studied.

We have extended our investigation to ascertain if immune blood affects the degree of phagocytosis in the infant's blood against *H. pertussis*. The exact methods of study and the results obtained constitute the material for a future report.

In summarizing the work completed to date, the following may be said: (1) The addition of convalescent, or of immune adult serum, to a mixture of newborn's blood and a suspension of *H. pertussis*, markedly increases the susceptibility of the organisms to phagocytosis by the polymorphonuclears leucocytes of the newborn's blood. (2) When infants are given such serum or blood intramuscularly or intravenously, the opsonizing power of the serum is increased in the majority of instances. (3) The opsono-cytophagic power of the blood increases during the course of whooping cough as was shown by Kendrick.[2] (4) It was approximately three times as great in a group of children (twenty-two in number) who had previously had the disease as in a similar group of twenty-two children who had never suffered from whooping cough.

References

1. Bradford, W. L.: Am. J. Dis. Child. 50: 918, 1935.
2. Kendrick, Pearl: Personal communication.

A Note on the Use of Reinforced Convalescent or Hyperimmune Serum for Passive Immunization of Infants Exposed to Pertussis

Dr. Pearl Kendrick

Even though pertussis vaccine should prove to be an effective agent for the active immunization of young children, we still have unsolved the problem of specific immunization in the infant from birth to the age at which we start active immunization. And it is in this very young age group that the death rate due to pertussis is so extremely high. A specific means of protecting the exposed infant is needed.

Various references are to be found concerning the use of convalescent blood for passive immunization against pertussis. The literature on the subject is reviewed by Bradford[1] in connection with a report of his own experience. He believes that immune blood probably is effective in the prevention or modification of whooping cough if given before the catarrhal symptoms appear.

So far as we have been able to discover, there has been but one report of an attempt to use a reinforced convalescent serum, that is a hyperimmune serum. Jundell[2] used the serum from an adult who had received several injections of pertussis vaccine—a maximum total of 7.5 c.c. of a one billion per cubic centimeter

suspension. The serum was given in the incubation or early stages of disease. The report included five cases which were considered mild in comparison with the primary cases in the family. While the data in his report are too few and indefinite to be judged by themselves, the underlying idea is worthy of trial.

Having obtained some inconclusive but suggestive results in exposed children following the use of convalescent serum from recently recovered donors, we decided to test hyperimmune serum as a possible means of preventing pertussis in exposed infants under one year—giving particular attention to the newborn baby in an infected family. An adult with a history of whooping cough in childhood was given a series of injections of a 10 billion per cubic centimeter suspension of *B. pertussis* vaccine, such as we are using in our immunization study.[3] The total quantity of vaccine has varied from 7.0 c.c. to as much as 20.0 c.c. over a period of time. The blood was collected about ten days after the last of a series of injections, and the processing of the serum included a final Mandler filtration. Each serum has shown agglutinins for *B. pertussis* and a very strong opsonic reaction. The dosage for the exposed infant has in general been 20 c.c.—10 c.c. as soon as possible after exposure was recognized and a second dose of 10 c.c. about ten days after the first, to cover the period of continued exposure.

To date we have completed histories for 22 infants under one year, 8 of them under one month. The exposure histories were definite in all, being familial in all but 3. Of these 22 infants, 17 were injected with serum, and 5 control babies received none. Of the 17 serum-injected infants, 11 were given the first dose of serum before symptoms of pertussis were recognizable, and 6 after symptoms had been present from one to eleven days. In the group of 11 serum-injected infants, pertussis did not develop in 9 of them, there was a light attack in one and a light to moderate attack in the other. The primary cases to which these 11 infants were exposed numbered 22, of which 8 were severe, 7 moderate, 6 light, and 1 very light. In the group of 6 infants injected with serum after symptoms were present, there were 1 light, 1 severe, and 4 moderate attacks of pertussis. Of the 7 primary cases to which these 6 had been exposed, 2 were severe and 5 were moderate.

It should be pointed out that the primary cases in the families with the serum-treated infants do not constitute true controls—they are in an older age group, and furthermore the real point to be controlled is the probable incidence of pertussis in the untreated, exposed infants. A pertinent question here is just what part the mother's immunity to pertussis plays in the protection of the newborn infant. The incidence of the disease in young infants as well as some unpublished results we have on opsonins in mothers and their infants would cast some doubt on the importance of the mother's immunity as a factor in the protection of the baby who has had an intimate exposure to pertussis. This point needs further study.

As true controls, we have to date only 5 infants who are in the same age group as the serum-injected children and have come to our attention during the study period. Two were newborn, 2 were eight weeks, and one was 6 months old. All were in families with one or more children in the early stages of whooping cough. Three of these control infants had severe attacks; two of them being critically ill. The fourth had a moderate attack, and the fifth escaped infection. In the last instance the mother made an effort to isolate the baby, and it is doubtful if the baby had an adequate exposure. The 8 primary cases to which the controls were exposed included 5 moderate and 1 severe, and 1 light, and 1 very light cases.

To summarize, we are beginning a study of the value of reinforced convalescent or hyperimmune serum for the prevention of pertussis in the exposed infant. We have in our series to date 22 under one year of age with definite history of exposure—17 who received serum and 5 control babies who did not. While the series obviously is too small to afford a basis for conclusion, it is encouraging

to note that in the group of 11 exposed infants who received serum before the onset of symptoms, only 2 developed pertussis. We believe that the possibility of such a serum having a place in the prevention of pertussis in the exposed infant merits the attention of interested workers who have the facilities for testing the procedure.

References

1. Bradford, William L.: Use of Convalescent Blood in Whooping Cough, Am. J. Dis. Child. 50: 918, 1935.
2. Jundell, I.: Has Specific Serum of Adults Any Value as a Remedy Against Whooping Cough? Acta Paediat. 15: 1, 1934.
3. Kendrick, P., and Eldering G.: Progress Report on Pertussis Immunization, Am. J. Pub. Health 26: 8, 1936.

Immunization With B. Pertussis Vaccine

(Progress Report)

L. W. Sauer, M.D.

Between 1928 and 1932, about 100 c.c. of vaccine were prepared at intervals of about two months, from five to seven hemolytic strains which had been isolated during the preceding weeks. The vaccine was refrigerated until used. About 200 fresh strains were used to make thirty-six lots of vaccine (1 c.c. = 10,000 million bacilli). In all, 394 selected, young nonimmune private patients were injected with a total of 7 to 8 c.c.[1] To date, 172 of them have been reported exposed, a total of 378 times. None is known to have contracted pertussis.

Since 1932, two laboratories have been authorized to prepare vaccine according to detailed specifications. For commercial reasons, several deviations from the original technic were necessary. The medium contains only 10 per cent human blood; the vaccine is not refrigerated while in transit; and the expiration date is one year. During the first two years, various Phase I strains were used for periods exceeding two months. The results are given in Table I.

TABLE I

IMMUNIZATION WITH AUTHORIZED COMMERCIAL VACCINE

		INJECTED*	EXPOSED		FAILED
Evanston health department (1933-)		865	68	{16 familial} {52 outside}	4
Private patients (1932-)		627	77	{35 familial} {42 outside}	6
Three orphanages (1932-)		252	57		6
"Cradle" infants (under 2 mo.)					
(1932-33)	6 c.c.	400	15	{8 familial} {7 outside}	6
(1934-)	8 c.c.	330	2		0
		2,474	219		22

*Children over three years of age now receive a total of 10 c.c. (1, 2, and 2 c.c. bilaterally).

If the 6 Cradle infants who contracted pertussis are excluded, only 16 of the 219 subsequently exposed children contracted the disease. It was light in 9, typical in 6, and severe in 1 child. Five of the children were more than three years of age when injected; 8 of the cases occurred in four households. An older infant, who contracted pertussis a year after injection, had received vaccine from the same lot as two older boys who developed the disease eighteen months after injection.

Seventy-four physicians in 24 states have reported their results; thirty-eight had written because they had one or more failures. A summary is given in Table II. It

TABLE II

RESULTS OF 74 PHYSICIANS IN 24 STATES

PHYSICIANS	INJECTED	EXPOSED	FAILED
13	1,147	---*	0
23	3,177	282	0
15	2,068	133	15 (1 failure each)
12	1,089	67	24 (2 failures each)
3	656	45	9 (3 failures each)
4	471	29	16 (4 failures each)
2	229	11	10 (5 failures each)
1	309	72	8
1	145	21	14
74	9,291	660	96

*No known exposures.

includes every reported failure. More than half occurred in children over three years of age when injected. The disease was light in many instances. Twelve physicians reported two, one reported three, and one reported four failures in a household. A physician in a city in the South reported 14 failures among 145 injected children; another physician in the same city used the same vaccine in 309 nonimmune children with 72 exposures and 8 failures. Several physicians wrote that their own children had been willfully, intimately, and repeatedly exposed more than four months after injection, without a failure.

Discussion.—Young children are very susceptible to pertussis. Because it is so prevalent, and often goes unrecognized throughout the most contagious stage, exposure is more frequent, intimate and repeated than smallpox, diphtheria, or scarlet fever. The immunizing power of an antigen depends upon its essential immunizing substance content at the time it is injected. Whether stock strains, kept under optimum conditions in the laboratory and grown on sheep's blood, will yield an antigen as potent as that made from five to seven recently isolated, hemolytic strains* will probably be decided within the next few years. The influence of intensive cultivation on the antigenicity of strains will receive further study. Little is known of such factors as heat, interrupted refrigeration,† and preservatives, on the stability of the immunizing fraction. Standardization of vaccine is not possible without a qualitative or quantitative test for this fraction. With no recognized test for immunity, occasional failures are quite inevitable. Agglutination and complement fixation tests have been proposed as guides in the selection of strains, also as an index of immunity conferred by vaccine. These tests are usually positive soon after the disease, also after the injection of vaccine into nonimmunes. In the latter, they are often positive before active immunity has been established. They become negative within a year or two after the disease or vaccine injection, i.e., when the humoral antibodies disappear. Immunity is more prolonged. Antigenicity is not identical with such antibacterial antibody response. Paterson, Bailey, and Waller[2] found that the intracutaneous injection of 0.1 c.c. of vaccine produces a positive skin test after the disease. A negative skin test in an immune individual becomes positive after the injection of 8 c.c. of vaccine. Whether this is an index of immunity has not yet been determined. If intimate exposures of children with negative tests prove them nonimmune, and similar exposures of children with positive tests prove them immune, the test will probably also be valuable as a biological test for the standardization of antigen. Intimate exposure to early pertussis remains the ultimate test of immunity. For the best results, vigilance is necessary in the selection of strains and in the preparation, preservation, and administration of the vaccine.

*In nearly four years, 141 freshly isolated strains have been sent to the one laboratory; in nearly three years, 117 fresh strains have been sent to the other.

†A chilled thermos food jar (½ pint) will keep cold vaccine cold for 24 hours.

References

1. Sauer, L.: Whooping Cough: A Study in Immunization, J. A. M. A. 100: 239, 1933.
   Immunization With Bacillus Pertussis Vaccine, Ibid. 101: 1449, 1933.
2. Paterson, D., Bailey, R., Waller, R.: Control of Whooping Cough With Serum and Vaccine, Lancet 229: 361, 1935.

Report on Krueger's Pertussis U.B.A. (Commercial)

J. M. Frawley, M.D.

Krueger's pertussis undenatured bacterial antigen has been used as a prophylactic agent before exposure, in prophylaxis after exposure, and therapeutically after coughing has begun.

1. As a prophylactic agent pertussis U.B.A. was given to two groups totalling 618 children. Five hundred and five children received 8.0 c.c., 113 received 12.0 c.c. Children in three groups who were subsequently exposed contracted whooping cough in a high percentage of cases, as shown in Table I.

TABLE I

SUMMARY OF PROPHYLACTIC VACCINATION WITH KRUEGER'S PERTUSSIS U.B.A. (COMMERCIAL)

DOSAGE	NO. OF CHILDREN VACCINATED	EXPOSURES		DEVELOPED WHOOPING COUGH		PERCENTAGE OF FAILURES
8 c.c.	505	Home	30	Mild	33	44.0
		School	68	Moderate	6	
			—	Severe	4	
		Total	98		—	
				Total	43	
12 c.c.	113	Home	9	Mild	6	47.6
		School	12	Moderate	1	
			—	Severe	3	
		Total	21		—	
				Total	10	

2. The published reports[1, 2, 3] on the use of pertussis U.B.A. as a prophylactic agent after exposure have been summarized by J. J. Miller.[4] The vaccine was used during the incubation period, in 98 cases; 50 per cent developed a cough. The cough in these cases was mild or atypical. It seems that the greatest benefit from pertussis U.B.A. is to be obtained when it is used in this manner.

3. The use of pertussis U.B.A. in treatment.

In a recent questionnaire replies were received from 162 pediatricians who had used pertussis U.B.A. in the treatment of over 3,700 cases of whooping cough. One hundred four (63 per cent) reported favorably.

However, in these cases no controls were used, and pertussis is a disease of such great variability that it is difficult to attribute good results to any particular agent unless there are adequate controls. Moreover, in many cases other agents besides pertussis U.B.A. were employed, e.g., sedatives, alternating doses of other vaccines, etc.

On the other hand, there is a definite feeling that in its present strength large doses should be employed (5 c.c. daily to children over one year of age, 2 c.c. to 5 c.c. to children less than one year) also that the best results are obtained when injections are begun either during the incubation period or the first day or two of coughing or else in the late stages after the disease has passed its peak. There is no certainty about the influence which may be expected when injections are begun during the height of the infection.

References

1. Frawley, J. M., Stallings, M., and Nichols, V. C.: J. PEDIAT. 4: 179, 1934.
2. Munns, G. F., and Aldrich, C. A.: J. PEDIAT. 5: 590, 1934.
3. Stallings, M., and Nichols, V. C.: Am. J. Dis. Child. 48: 1183, 1934.
4. Miller, J. J.: Report on Pertussis Undenatured Bacterial Antigen (Krueger) Given Before the Laboratory Section of the Am. Pub. Health Assn., Milwaukee, October, 1935.

GENERAL DISCUSSION

DR. TOM MITCHELL (MEMPHIS, TENN.) questioned Dr. Sauer as to his method of sterilization of syringes and needles.

DR. SAUER favors and uses only the method of dry sterilization in oven rather than boiling. He stores his sterile needles in gauze-packed test tubes.

DR. A. G. HELMICK (COLUMBUS, OHIO) asked Dr. Sauer whether artificial immunization for pertussis may not be greater than that of natural immunization.

DR. SAUER did not know.

DR. F. B. MINER (FLINT, MICH.).—Why distribute dosage in both arms?

DR. SAUER.—The dosage is distributed in both arms because the reactions appear milder. The first dosage of 2 c.c. can safely be given in one arm. Give the injections subcutaneously near the skin and not intramuscularly. It is desirable to feel a nodule from one to two weeks after injection.

DR. F. R. JANNEY (WAUWATOSA, WIS.) stated he has immunized more than 300 infants with Sauer's vaccine by injecting all of each dose in one arm instead of using both arms. He has seen no untoward effects.

DR. C. O. TERRELL (FORT WORTH, TEXAS) questioned Dr. Sauer as to why it is necessary to refrigerate his commercial vaccine.

DR. BRADFORD.—I have been greatly interested in the plea of Dr. Sauer for extreme precaution in the proper refrigeration of the vaccine, and, of course, subscribe to this idea, but I should naturally wonder why a commercial whooping cough vaccine should require greater precautions as regards refrigeration than does, let us say, a commercial typhoid vaccine.

DR. SAUER advises that the vaccine be kept in the refrigerator at all times. Failures of immunization have been noted in cases in which the vaccine used has been kept on the shelf in the home or in the physician's bag. When the physician does the immunization in the home, it is advisable to transport the vaccine in a half-pint vacuum food container.

CHAIRMAN HUENEKENS.—Where can this portable container be obtained?

DR. SAUER.—Either through your druggist or at a hardware store.

DR. TERRELL.—Is there any scientific reason why diphtheria toxin and pertussis vaccine cannot be given two or three weeks apart?

DR. SAUER.—As far as is known there is no contraindication for following diphtheria toxoid with the pertussis vaccine and vice versa. We allow four-month intervals between the pertussis inoculations, diphtheria toxoid, and smallpox vaccination. This is done so we can be sure one does not interfere with the other for statistical purposes. The pertussis vaccine should be given first usually around the sixth month. It is not necessary to hurry all these immunizations.

DR. GILBERT J. LEVY (MEMPHIS, TENN.) gives the vaccine between the fourth and eighth months.

DR. MURPHY immunizes with Sauer's vaccine not later than the fourth month.

DR. F. C. NEFF (KANSAS CITY, Mo.) asked a question relative to the occurrence of second attacks of whooping cough.

DR. TERRELL stated he had had several cases in which mothers and nurses who had previously had whooping cough developed mild coughs while taking care of a child with whooping cough.

DR. BRADFORD.—In support of Dr. Neff's contention that second attacks of whooping cough may easily be missed, I should like to refer to a case recently observed in the private practice of Dr. Daniel Landau, in Rochester, in which the cough was very mild, lasting less than ten days; yet a typical Phase I organism was isolated by the cough-plate method. The attack was supposedly primary and occurred in a young boy exposed to known cases of whooping cough in his schoolroom. A more accurate method of determining immunity such as a dermal reaction would be of great assistance in such cases.

In connection with the remarks of Dr. Terrell concerning the incidence of whooping cough among mothers, the studies reported by Christensen are of interest in that he found that about 3 per cent of case contacts showed the presence of the bacillus on culture.

DR. SAUER stated that in his experience grandmothers were most frequently affected, mothers less often, and fathers rarely. He knows of only one case of recurrent whooping cough in childhood.

DR. TERRELL.—What are the best therapeutic measures? Results with vaccine as a therapeutic measure?

DR. SAUER.—The following three procedures are better than vaccines: (1) 25 per cent ether in olive oil inserted into the rectum with a catheter. One tablespoonful of this mixture two or three times daily is usually sufficient; (2) rest in bed one to two weeks; (3) avoidance of infections.

I cannot express an opinion relative to the value of vaccine given early. Some physicians give dosage at four-day intervals during the incubation and catarrhal stages. I do not believe any harm can be done with the vaccine; some individuals develop immune bodies in varying lengths of time from one to four months.

DR. TERRELL.—In twenty cases in which a vaccine was given at the beginning of exposure, all resulting cases were very mild.

DR. BRADFORD.—The favorable results obtained by Dr. Terrell from vaccine administered to the exposed child may in part be explained by the work of Kendrick who showed that an increase in the phagocytic power of the blood occurred as early as ten days after injection of vaccine.

CHAIRMAN HUENEKENS.—Vaccine gives partial immunity before the fourth month following inoculation so we should keep an open mind relative to the use of vaccine as a therapeutic agent. It should be used only during the incubation and catarrhal stages. I agree with measures outlined by Dr. Sauer.

DR. H. D. PYLE (SOUTH BEND, IND.).—What is the definite way of gauging dose of ether?

DR. SAUER.—It is best to give one tablespoonful of 25 per cent ether in olive oil regardless of age except in the older child, in whom a double dose can be used.

DR. TERRELL asked a question relative to therapeutic results of Krueger's endoantigen.

DR. PYLE, DR. THOMAS, AND DR. STRINGFIELD all reported definite benefit in over 50 per cent of their cases. Dosage of 2 c.c. was given at two-day intervals in from five to eight inoculations.

DR. O. L. STRINGFIELD, Recorder.
Stamford, Conn.

REPORT OF THE COMMITTEE ON HOSPITALS AND DISPENSARIES

Contagious Disease Hospitals

Part I

Chairman, Dr. Clifford G. Grulee; Secretary, Dr. George F. Munns; Dr. Murray H. Bass, Dr. Laurence R. DeBuys, Dr. Henry Dietrich, and Dr. Lewis Webb Hill.

THE first report in the following series will concern contagious disease hospitals found in Region III of the Academy of Pediatrics. Questionnaires were sent to thirty-eight institutions in this region which were listed as contagious disease hospitals. Thirty-five were returned, but among this number were several reports which indicated that the institutions would hardly be described by the name of contagious disease hospital. Perhaps "pesthouse" would be more suitable. The replies of some other hospitals were so incomplete that they were of no use to us in compiling this report. In other sections certain portions of the questionnaires were not filled out, hence as each section is discussed we shall indicate the number of hospitals which replied to that section.

Region III

Hospitals

Table I

KEY NO.	NAME
1	City Isolation Hospital, Colorado Springs, Colo.
2	Steel Memorial Hospital, Denver, Colo.
3	Municipal Contagious Disease Hospital, Chicago, Ill.
4	Evanston Hospital, Evanston, Ill.
5	City Contagious Hospital, LaSalle and Peru, Ill.
6	Fort Wayne and Allen County Isolation Hospital, Fort Wayne, Ind.
7	St. Anthony's Hospital, Contagious Section, Carroll, Iowa
8	City Isolation Hospital, Council Bluffs, Iowa
9	City Isolation Hospital, Grinnell, Iowa
10	City Isolation Hospital, Sioux City, Iowa
11	Herman Kiefer Hospital, Contagious Disease Division, Detroit, Mich.
12	Municipal Isolation Hospital, Grand Rapids, Mich.
13	Jackson County Contagious Hospital, Jackson, Mich.
14	Lansing City Hospital, Lansing, Mich.
15	Oakland County Contagious Hospital, Pontiac, Mich.
16	Port Huron Emergency Hospital, Port Huron, Mich.
17	Saginaw County Contagious Hospital, Saginaw, Mich.
18	Minneapolis General Hospital, Contagious Dept., Minneapolis, Minn.
19	Ancker Hospital, Contagious Department, St. Paul, Minn.
20	City Isolation Hospital, St. Louis, Mo.
21	Isolation Hospital, Lincoln, Neb.
22	Municipal Hospital for Contagious Diseases, Omaha, Neb.
23	Cincinnati General Hospital, Cincinnati, Ohio
24	Cleveland City Hospital, Contagious Hospital, Cleveland, Ohio
25	Quarantine Hospital, Dayton, Ohio
26	Municipal Hospital for Contagious Diseases, Toledo, Ohio
27	City Detention Hospital, Aberdeen, S. D.
28	City Detention Hospital, Sioux Falls, S. D.
29	Beloit Detention Hospital, Beloit, Wis.
30	City Isolation Hospital, Green Bay, Wis.
31	Detention Hospital, Janesville, Wis.
32	Isolation Hospital, Madison, Wis.
33	South View Hospital, Milwaukee, Wis.
34	Lincoln Memorial Hospital, Racine, Wis.
35	Isolation Hospital, Superior, Wis.

In general the form of the questionnaire is the same as that used by the committee in previously published reports concerning general and children's hospitals.

1. Staff: Professional Staff—Attending Staff.—Among 25 hospitals 11 report that ward patients are under the exclusive care of the attending staff. Nineteen report that all physicians in the community are permitted to send patients to the wards and treat them there. This disagreement in figures is probably accounted for by the custom of allowing only members of the staff to care for so-called service (free or semifree) cases which usually go to the wards, but a few private cases may also go to the wards, and their own physicians are allowed to care for them there. Only 12 replies were received concerning qualifications permitting nonstaff physicians to attend patients in the hospital. All of them require the attending man to be a licensed physician in good standing.

Information concerning attending physicians in the various specialties is best presented by Table II.

Among 20 hospitals which replied, the attending staff is full-time in 6, but among several of these (4) the claim was based on the fact that a resident physician or health officer was in charge. The attending staff was stated to be salaried in 11 instances, but in at least 7 instances this seemed to apply to only one man, and he in turn often was the city health commissioner.

TABLE II

	NUMBER OF REPLIES	HAVE SPECIALISTS ON ATTENDING STAFF	HOW MANY?	VISIT AT REGULAR INTERVALS IN?	ON CALL ONLY IN?
Pediatrics	16	13	2-8	5	8
Otolaryngology	18	16	1-5	5	10
Orthopedics	16	12	2-8	2	12
Ophthalmology	16	14	2-3	2	12
Oral surgery	14	9	1-2	2	11
Oral hygiene	14	8	1-2	2	10
Roentgenology	15	10	1-5	3	10
Pathology	15	12	1-4	3	10
Allergy	15	9	1	1	10
Surgery	17	15	2-15	2	13
Neurology	16	12	2-7	2	13
Psychiatry	16	12	2-5	1	11
Dermatology	15	12	1-5	3	13
Dentistry	14	10	1-4	4	10
Psychology	16	10	2-3	1	10

House Staff.—Twenty-five hospitals replied to this section of the questionnaire. Nine employ residents; 15 have no resident; 1 did not reply. In 6 institutions women are eligible for this position. Salaries are paid in 8 instances. These salaries vary from $30 per month to $900 per year. Four hospitals require a preliminary general interneship of one year. One hospital requires a previous experience of one year of general interneship and one year of work as assistant resident in contagious work. One requires two years of hospital experience including at least one year in pediatrics. In 2 instances the position is included as part of a general interneship, and 1 hospital employs a senior medical student in that capacity. The usual term of the service is one year except in 2 instances in which contagious service is part of a general interneship. The period is for six weeks in one and six months in the other. The resident has dispensary duties in only 4 instances.

Only 4 hospitals employ assistant residents. Women are eligible for this service in 2 hospitals. All pay the assistant resident a salary. All require previous experience consisting of one year of general interneship. The service is for one year

in 2 hospitals, six months in 1, and ten weeks in another. Assistant residents have dispensary duties in 3 hospitals. Thirteen hospitals employ internes; 12 do not, the number varying from 1 to twelve. Six employ more than 2, one as many as 32, the next highest in order being 12, 8, and 6. Only 10 hospitals replied concerning eligibility of women for interneship. Women are eligible in 8 of these. Salaries are paid to internes in only 1 instance. Ten replied concerning qualifications for interneship. All require a degree from a Class A medical school. None require previous hospital experience. The length of the service varies from eight weeks to one year. One offers ten-day periods of service during the busy months.

Educational Activities.—These are presented in Table III.

Twenty-five hospitals replied to this section of the questionnaire. Among these only 7 are connected with medical schools. Clinics are given to medical students in 8, while ward rounds are offered for medical students by 10.

Special Information is presented in Table IV with summary.

Newly admitted patients are retained in observation wards in 10 hospitals. Two of these report that a cubicle system is used. Ten do not retain patients in an observation ward. Six did not reply. Nine report that patients are usually retained in an observation ward until the diagnosis is made or "as long as necessary." There were only 4 replies to the question concerning procedure before admission. Among 19 hospitals all but 1 take routine throat cultures for *B. diphtheria;* 1 takes cultures "as indicated." Thirteen culture routinely for *Streptococcus hemolyticus;* three, "when indicated." Routine vaginal smears are done in 14 "when indicated"; von Pirquet tests, in three; Wassermann or Kahn tests, in two; Schick and Dick tests, in seven and six, respectively. Routine blood counts are taken in 10. Urinalyses in 19, and routine history and physical examinations are done in 18 and 16, respectively.

Superintendent.—Nineteen hospitals replied to this section of the questionnaire which concerns the physical set-up of the hospitals. Seventeen of these hospitals are located in residential districts and 16 of these in better or middle-class districts. Only 1 is found in a tenement district. Five are located in factory districts and 3 in shop districts. All but 2 are not in noisy districts. These 2 report that there is noise from both factories and heavy traffic. Two are located on unpaved streets; the remainder report that the pavements near them are smooth.

Tables V and VI give the more interesting details concerning the physical organization, size, etc., of these hospitals.

Quickly summarizing these tables we find that some of these hospitals are quite large and many are small. Only 3 have 10 or more buildings while 15 have one or two. Some are old, dating from 1883, many are fairly modern. Only 3 were constructed prior to 1900. Most of these buildings are not large, 15 hospitals reporting that they have one or two floors. Among 24 hospitals only 13 are reported to be fireproof. Six report that they have fire stairs and 12 that they have outside fire escapes; 11 and 7 hospitals, respectively, do not reply to the latter 2 questions. "Cost of buildings" needs no comment except that wide variations here probably indicate size and modernity of the plants. Bed capacities among 22 hospitals which replied vary from 16 to 1,000. Eleven, or one-half, possess bed capacities of 50 or less, 8 have 100 or more. The 3 largest report 1,000, 681, and 500 bed capacities. The 3 smallest, 4, 10, and 10. Eleven report the number of cribs available. These vary from a number as low as 3 to as high as 228, the 3 highest being 228, 150, and 68, and the lowest 3, 4, and 6.

Of 15 hospitals which replied, 14 have wards. Six indicate that they have cubicles containing 1, 2, 3, or 4 beds. Seventeen exclude no type of contagious disease. Two exclude smallpox; one, erysipelas; one, measles, chickenpox, and pertussis; and one, tuberculosis, typhoid fever, and venereal disease.

TABLE III

EDUCATIONAL ACTIVITIES

	HOSPITAL CONNECTED WITH MED. SCHOOL	CLINICS GIVEN MED. STUDENTS	WARD ROUNDS OR WALKS GIVEN FOR MED. STUD.	CLINICS OPEN TO PRACT. PHYS.	NO. AND CHARACTER	WARD ROUNDS OR WALKS OPEN TO PRACT. PHYS.	NO. AND CHARACTER	DEFINITE COURSES OF POSTGRAD. INSTRUCTION	LIMITED NUMBER	ENROLLMENT LAST YEAR	THIS YEAR	LENGTH OF COURSE	HOURS	CLINICAL CONFERENCE FOR INTERNES	HOW OFTEN	PATH. CONF. HELD FOR INTERNES	HOW OFTEN	MEDICAL LIBRARY	NO. VOLUMES	RESEARCH FACILITIES AVAILABLE TO RES. AND HOUSE STAFF	DESCRIBE BRIEFLY	RESEARCH PROJECTS IN COMMUNICABLE DISEASE ENCOURAGED
1	no	no	no					no						yes	1 per mo.	yes	once a mo.	yes	38	clin.		yes—cases reported to med. journals
2	yes	yes	yes	no		no		no						yes	2 per wk.	yes	irregularly	yes	0	Av. lab. fac. for any res. (but not the best)		
3	no	no	yes	no		no		no						yes	no reg. time	yes	monthly	yes	100	ltd.		yes
4	yes	yes	yes	staff only				no						yes	weekly	yes	weekly	yes	3,100	ltd.		yes
7	no	no		no				no											0	no		no
8	no			no		no		no											0			
9	no	no	no	no		no		no											0			
10	no	no	no	no		no		no											0			
11	yes	yes	yes	yes	1 per wk. in early part of yr.	yes	as many as requested	yes	to all phys.	250	250	5 wk.	2 hr. per wk.	yes	bi-weekly	yes	weekly	yes		yes	private lab.	yes

Blank spaces in chart indicate that there was no reply.

Blank spaces in chart indicate that there was no reply.

TABLE III—CONT'D

12	no	no	no	no		yes		no														yes
14	no	no	no	no		no		no														no
15	no	no	no	no		no		no														
16	no	no	no	no		no		no														
17	no	no	no	no		no		no														
18	yes	yes	yes	occa-sion-ally		no		no						no		yes	weekly	yes	30	clin.		yes
19	yes	yes	yes	no		yes		no						yes	daily	yes	weekly	yes	jour-nals only	clin.		not dis-couraged
20	no	yes	yes	yes	1 series of 5 clin.	yes	daily infor-mal	no						yes	weekly	no		yes	10	yes	clin.	yes
21	no	no	no	no		no		no														
22	no	no	no	no		no		no						yes	as re-quired	yes	as re-quired	no	none	no		yes
23	yes	yes	yes	yes		yes		no						yes	weekly	yes	weekly	yes	40,000	yes	as-signed def. prob.	yes
24	yes	yes	both	no		yes	twice w'kly	no						yes	weekly	yes	weekly	yes	4,000	yes	clin.	yes
31	no	no	no	no		no		no											none			no
32	no	no	no	no		no		no														no
33	no	no	yes	no		occa-sion-ally		no						yes	daily	yes	daily	yes	12			yes
35	no	no	no	no		no		no														no

TABLE IV

SPECIAL INFORMATION

	ARE CASES RETAINED IN OBSERV. WARD	HOW LONG MAY THEY BE KEPT	PROCEDURE BEFORE ADMISSION	THROAT CULTURE FOR B. DIPH.	THROAT CULTURE FOR HEM. STREP.	VAG. SMEARS FOR GONOCOCCI	VON PIRQUET OR MANTOUX	WASSERMANN OR KAHN	SCHICK TEST	DICK TEST	ROUTINE BLOOD COUNTS	URINALYSIS	HISTORY TAKEN	COMPLETE PHYS. MADE
1	Depends on case	As long as phys. desires	Diag. made by phys.	Yes	Yes	Yes	Yes by int.	Yes	Yes	Yes	At phys. request	Routine	Complete hist. kept	Yes
2	N.R.*	Indefinite	Phys. exam. & culture	Yes	Yes	Not unless indicated	No	Wass. only	No	No	Yes	Yes	Yes	Yes
3	None	Cubicle system used		Yes	Not always	Yes	No	Yes for adult scarlets	No	No	Yes	Yes	Yes	Yes
4	Until report from T.C. and vag. smear			Yes		Yes	No	No	No	No	Yes	Yes	Yes	Yes
7	N.R.			Yes	No	Yes	Occasionally	If indicated	Yes	Yes	Yes	Yes	Yes	Yes
8	None													
9	None							No				Yes	Yes	Yes
10	None													
11	Cubicle system	Until diag. is confirmed		Yes	Yes	Yes	When indicated	Yes	When indicated	When indicated	Yes	When indicated	Yes	Yes Vac. for smallpox

*N.R., no report.

*N.R., no report.

TABLE IV—CONT'D

12	N.R.													
14	As long as nec.			Yes	Yes	Yes	No	No	No	No	No	Yes	No	No
15	Yes	3 days to 2 wk.		Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
16	None			Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	Phys. takes care
17	Until positive diag. is made	Not longer than necessary	Bath, shampoo, physical	Yes	Yes	Yes	On suspected cases	When ordered	When ordered	When ordered	When ordered	Yes	Yes	Yes
18	N.R.	As long as nec.		Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes
19	N.R.			Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes
20	1 day	As long as nec.		Yes	No	No	If indicated	Yes	Yes	No	Yes	Yes	Yes	Yes
21	None													
22	N.R.			Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes
23	Cubicle			Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes
24	7-14 days	B. of H. release		Yes	Only if indicated	If indicated	Only in meas. B. & whoop. cough	If indicated	No	Yes	Where indicated	Yes	Yes	Yes
31	None			Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	No
32	Long as nec.		3 cultures, nose and throat	Yes	Yes	No	No	No	No	No	No	Yes	Yes	Up to phys.
33	None			When indicated										
35	None			Yes	Yes	Yes	Available	Yes	Yes	Yes	No	Yes	By phys.	Phys.

TABLE V

SUPERINTENDENT

	NO. OF BLDGS. IN PLANT	DATE OF CONSTRUCTION	DATE OF ADDITION	NUMBER OF FLOORS	FIREPROOF	FIRE STAIRS IN WALLS	OUTSIDE FIRE ESCAPE	COST OF BUILDINGS	BED CAPACITY	TOTAL NO. OF BEDS	CRIBS	BEDS	WARDS	CUBICLES	NO. BEDS IN EACH CUBICLE	EXCLUDE TYPE OF CONT. DIS.	TYPE
1	2	1918	None	3	Yes	Yes			16	16	3		4	None		Yes	Smallpox
2	5	1908	None	2	Partially		1		85	85	8	25	12	2			
3	7	1916 1919 1930		3 & 5	Yes	1	Yes	$2,082,000			228	200	34	4	2	Yes	Measles, erysipelas, smallpox, whooping cough, chickenpox
4	11	1898 1930		3 & 5	Yes		Yes			50	25	25		Yes	1		
7	1	1915	None	1	Semi					4	2	4	None			No	
8	1			2	No					10			2	None		No	
9	2	1919	None	4 & 2	Yes		Yes	90,000		15						No	
10	1			2	No	No	No		25	25							
11	11	1910 1911 1912 1913 1918 1922 1925 1928		2 3 4 7	Yes	Yes	Yes	8,000,000	500				7	Yes	1-4	No	

TABLE V—CONT'D

12	2	1910		1	No				50				4			No		
14	1	1921	1925	1	Semi	No	No	25,000	60	10	50					Yes		
15	2	1926		2	Yes	Yes	Yes	150,000		80	20	16	4			No		
16	1	1922		2	No	No	Yes	20,000		24	6	18				No		
17	1	1930		3	Yes		No	174,000	99				14	None		No		
18	6	1916		8	Yes		Yes	1,800,000	681				6	4	1	No		
19	12	1883 1927	1927	2-5	Yes	Semi	Yes		1,000	1,000						No		
20	4	1915 1926		2	Yes	No	No		250		150	100	8			No		
21										24						No		
22	1			3	No	Yes	Yes			40			3			Yes		
23	5	1915		2	Yes				150	150			7	5	3	No		
24	2	1910 1922		7	Yes	Yes		600,000	196	150			7	4	1	No		
31	1				No	No	No									No		
32	1	1923		3	Yes	Yes	Yes	150,000		54	4	50				No		
33	3	1911 1915 1919		2	Semi		Yes	586,310		250	68	25	18			Yes	Tuberculosis, typhoid fever, venereal disease	
35	2	1896 1921		2 & 1	No	No	Yes	19,184		17		17				No		

Only 15 hospitals reply to the section concerning observation wards. Thirteen have them, that is, either wards, rooms, or cubicles. Two have none of these.

Contagious Diseases Wards.—Among 17 hospitals replying, 16 have wards (one or more) with a total bed capacity of 1,303 (Table VI). The number of beds in wards vary from 1 to 21. Five have cubicles, and 12 have private rooms with a total bed capacity of 317. Nineteen have sunlight, and 10 have outdoor porches. Children and adults are placed in the same wards in 10 hospitals. In several instances these cubicle systems are used on the wards.

TABLE VI

SUPERINTENDENT

CONTAGIOUS DISEASE WARDS

	NUMBER WARDS	NUMBER BEDS	NUMBER BEDS IN WARDS	CUBICLES	SEPARATE ROOMS	SUNLIGHT	OUTDOOR PORCHES	ADULTS AND CHILDREN IN SAME WARD
1	2	12	2 W. 4 Porches	None	2 semi-private	East & west	1	No
2	4	65	Varies			Yes	Yes	Yes
3						Yes	No	Yes
4		20		Yes		Yes	Yes	No
7	None							
8								
9	7	15	2-3			Yes	No	No
10								
11	7	500	15	115	115	Yes	Yes	No
12								
14	5	50	2-16		3	Yes	No	Yes
15	8	80	10		8	Yes	No	Yes
16		24	2		9	Yes	1	No
17	7	56		None	10		No	Occasionally
18	2	46	4-5	4, 4-5	20	Yes	Yes	Occasionally
19					20	Yes	Yes	No
20	8	20-40			48	Yes	8	Yes
21								
22	3	40	1-8		16	Yes	No	Yes
23	7	150	21	11-15		Yes	Yes	Yes
24	7	196	3-4	164	64	Yes	Yes	No
31	1	3			4	Yes	No	No
32	2	16	4			Yes	No	No
33						Yes	No	Yes
35						Yes	No	No

Admissions.—Admission figures for hospitals listed by number for the years 1932, 1933, and 1934 are presented in Table VII.

Admission figures clearly indicate that comparatively few of these institutions are large; only 6 report admission of 5,000 or more in any one year. Two of these admitted that many patients during only one year each, and one apparently confused contagious disease hospital admissions with total admissions to the general hospital of which it is a part. Eight hospitals during at least two of the three years concerned admitted 100 or fewer patients, and exactly one-half of the total number of hospitals which replied have fewer admissions for any one of the three years.

The percentages of deaths for all hospitals were 6.4, 6.3, and 5.6 for the years 1932, 1933, and 1934, respectively.

Both white and negro children are admitted to 22 hospitals of 23 which replied. Nine hospitals segregate white and negro patients. None of them limit the number of negro patients that may be admitted. However, the proportion in all but one is very small. This one reports 20 per cent.

An attempt was made to determine the number of available charity beds among these hospitals, but only 9 replied to this query. Two report "all"; two, 90 per cent and 95 per cent; the remainder, 50, 150, 500, 681, and 1,000 beds, respectively. Replies to the question concerning "pay beds" were equally incomplete. Three reported none, these being the largest of all the hospitals and municipal institutions in each instance. There were only 4 replies to the question concerning the number of private rooms for children. Two have them; 2 do not; probably these are available in many of the hospitals but are not used for children only. There are facilities for accommodation of mothers in case they desire to stay in the hospital with sick children among nine hospitals.

Finances.—No hospital among the 23 institutions which replied derived funds from the state. Twenty of these derive their funds entirely from city or county or both. Two report that they are entirely supported by private contributions. No hospital reports income from an endowment or from the community chest.

The cost of running these hospitals, of course, varies with the size. The lowest cost reported was $500; the highest, $903,788 for the year 1934. Cost per patient per day varied among 16 hospitals which replied from $1.82 to $5.50.

Information requested concerning detailed costs such as, interest on investment, land, teachers' salaries, etc., was forthcoming in so few instances that no report can be made. Only 4 reported the average daily cost per patient for food. This sum varied from $0.58 to $2.89. Only 2 replies were received concerning cost of nursing and supplies.

In 13 hospitals the superintendent is a man, and in nine, a woman. In 10 instances the superintendent is a physician; in 6, a layman; and in 7, a registered nurse. In no instance do the superintendents have charge of the nurses' training school if one exists.

Nursing (General).—Among 25 hospitals which replied, 11 are affiliated with other hospitals for the purpose of special training in nursing. Eleven offer courses in contagious disease nursing technic. The length of the courses varies from three weeks to three months. Two courses are for four weeks, one for three weeks, the remainder are for two or three months. One offers a four-month postgraduate course. Fifteen hospitals employ only graduate nurses. Immunization of nurses to diphtheria is done in 23, to scarlet fever in 14, to smallpox in 23, and to typhoid fever in 8. Nurses contracted diphtheria (1934) in 2 hospitals (16 in 1, 2 in the other) and scarlet fever in 7 hospitals, the number affected being 2, 3, 13, 1, 3, 1, and 3, respectively. Other contagious diseases were contracted by nurses in 9 hospitals; these infections were usually German measles, measles, and mumps. One nurse contracted smallpox.

Training.—About half the hospitals failed to reply to questions concerning the number of day and night nurses on duty and the length of their assignments. Many of those which did reply interpreted the question "length of assignment" to mean "period of time on the service" rather than "number of hours on duty each day." Hence figures for this portion of the questionnaire are most unsatisfactory and noninstructive and are omitted.

Operating Room.—Fifteen hospitals have at least 1 special operating room, and only 2 assign student nurses for duty there. These are assigned for a two- or three-month period. The number of operations performed during 1934 is reported by only 14 hospitals, and again one of these does not report figures for the contagious

TABLE VII

ATTENDANCE

	PATIENTS ADMITTED			PATIENTS DISCHARGED			DIED IN HOSPITAL			NO. IN HOSP. OPEN FISCAL YEAR	NO. IN HOSP. CLOSE FISCAL YEAR	WHITE AND COLORED CHILDREN
	1932	1933	1934	1932	1933	1934	1932	1933	1934			
1	78	58	126	71	64	126	8	4	16	3	3	Yes
2	632	650	706	625	468	636	32	14	22			Yes
3	3,154	3,832	4,405	2,923	3,669	4,238	130	119	152	333	348	Yes
4			5,857†			5,695†			117†	117†	162†	No
7	9	25	16							4	1-2	Yes
8	122	77	60				1	1	2			Yes
9	1	3	5	1	3	5	0	0	0	0	1	Yes
10	98	75	80				1	2	0			Yes
11	5,374	4,061	3,312	5,314	4,293	3,398	316	267	189	164	78	Yes
12	110	114	310	*119	109	303	*Included in 119	5	3	9	13	Yes
14	152	319	309	146	302	323	0	3	4	25	7	Yes
15	798	703	806		678		41	43	16	29	24	Yes
16	55	26	30	50	23	29	5	3	1	1	9	Yes
17	376	281	250	320	260	224	39	35	29	33	35	Yes
18	13,665	14,179	13,768	13,467	13,884	13,672	1,031	1,004	957	459	509	Yes
19	12,617	12,045	12,387	11,071	10,514	11,523	802	815	899	762	730	Yes
20	2,105	1,942	5,003			2,629	159	142	304	224	167	Yes
21		5	2		5	2		0	0			
22												
23	961	1,088	1,413	940	956	1,281	73	62	146	96	98	Yes
24	2,348	2,280	1,758	2,148	2,080	1,608	146	123	123	115	83	Yes
31			3			3			0	3	0	Yes
32	111	92	174			170			4	4	15	Yes
33	860	876	2,624	907	852	2,482	19	25	20	55	24	Yes
35	22	10	25	22	9	24	0	1	0	0	2	Yes
Total	43,648	42,741	53,629	38,124	38,169	48,371	2,803	2,698	3,004	2,436	2,499	

division alone. One hospital reports 5,271 operations, another, 331; a third, 269; the remainder, fewer than 100, and among the latter only one reports more than 50—in other words 10 had performed 50 or fewer operations.

Diet Kitchen.—Only 4 hospitals report that they have diet kitchens for infant foods. Four others use the diet kitchen of a general hospital of which the contagious division is a part. Only 3 report that student nurses work in these kitchens. Their period of service usually is from one to two weeks. Only 2 hospitals indicate that training is given in the preparation of children's diets. Fourteen did not reply.

Supervision.—Ten hospitals report that a head nurse is employed for each ward. Seventeen do not reply. As a rule, there is a proportion of one graduate assigned to each ward, and this proportion applies to night nurses as well, except in two instances in which only student nurses are used.

Nursing.—An effort to obtain information concerning the number of hours of instruction in contagious disease nursing was not very successful. Only 12 hospitals replied, and of these only 5 give a course of lectures in that subject. The courses vary from ten to thirty-two hours, and the instruction usually consists of both lectures and demonstrations. Courses are conducted by members of the medical staff. Only 3 hospitals indicate that demonstrations in contagious disease nursing are given. Only 3 offer postgraduate courses. In general, very little information was offered relative to training for contagious disease nursing, except by hospitals connected with medical schools.

Rather few hospitals replied to questions concerning cross-infections during year 1934. The information that was given is as follows:

Diphtheria: Eight replied; one hospital had 1 cross-infection; 1 had 3; and 6, none.

Scarlet fever: Eight replied; 3 had 2; 2 had 3; and 3 had none.

Measles: Eight replied; 1 had 50, 1 had 5, 2 had 1, and 4, none.

Pertussis: Eight replied; 1 had 1; 1 had 3; 1 had 2; and 5, none.

Chickenpox: Nine replied; 1 had 41; 1 had 23; 1 had 7; 1 had 5; 1 had 1; and 4, none.

Other diseases: Seven replied; 1 had 14; 1 had 13; 1 had 1, and 4, none.

Information concerning x-ray facilities is given in Table VIII.

Eleven hospitals indicate that they have neither an x-ray department nor diagnostic facilities. From one there was no reply. Only 1 hospital has a separate x-ray department, but 13 have available diagnostic facilities at any hour, day or night, and in 11 instances full-time technicians are available. Eight are equipped for high speed radiography with milliamperage as indicated in Table VIII. Ten are equipped for superficial radiography at the voltage indicated in the table. Only 4 are equipped for deep radiotherapy with voltage as indicated on chart. Thirteen have a fluoroscope, 10 can make stereoscopic plates and 10 have a portable x-ray machine. Internes do not do x-ray work in any of these hospitals. Ten among 15 hospitals which replied consider their x-ray facilities to be adequate. The x-ray department serves the dispensary in 6 hospitals and outside physicians in 9. However, we believe that many of these departments are located in general hospitals and serve the entire hospital including the contagious disease division. With this thought in mind, we believe that figures given for the number of x-ray plates, treatments, etc., during the last fiscal year are not confined to the contagious disease department alone and hence are not very illuminating as far as this report is concerned.

Laboratories (Pathologic, Clinical, Bacteriologic, and Serologic).—There was no reply from five hospitals among twenty-six from whom we received questionnaires, and, as usual, among the 21 there was a number which failed to reply to all questions.

TABLE VIII

X-RAY

	IS THERE AN X-RAY DEPT.?	DIAGNOSTIC FACILITIES	NO. FULL-TIME TECHNICIANS	FACILITIES AT ANY HOUR, DAY OR NIGHT	WHAT HOURS?	EQUIPPED FOR HIGH SPEED RADIOGRAPHY	WHAT MILLIAMPERAGE?	EQUIPPED FOR SUPERFICIAL RADIOGRAPHY	WHAT VOLTAGE?	EQUIPPED FOR DEEP RADIOTHERAPY	WHAT VOLTAGE?	FLUOROSCOPE	MAKE STEREOSCOPIC PLATES	PORTABLE X-RAY MACHINE	INTERNES			ARE FACILITIES ADEQUATE? IF NOT, HOW?	DEPT. SERVE DISP.	SERVE OUTSIDE PTS.	NO. OF X-RAY PLATES LAST FISCAL YEAR	NO. SUPERFICIAL TREATMENTS	NO. DEEP THERAPY TREATMENTS
															DO X-RAY WORK	ROUTINE	SPECIAL						
1	yes	yes	2	yes	all	mod.	100	yes	75	yes	180	yes	yes	yes	no	no	no	want higher Ma. for Radiotherapy & deep therapy		yes	2,779	13	57
2	Denver Hosp.	yes	3	yes		yes		no		no		yes	yes	yes	no			except therapy	yes	no	exposures 21,776	0	0
3		yes	0	yes		no		no		no		yes	no	no	no			yes	no	no	85	0	0
4		yes	3	yes	all	yes	100	yes	50–130	yes	180	yes	yes	yes	no	no	no	yes	yes	yes	Exams. 5,370		
7		yes	1	yes		yes	?	yes	?	no		yes	yes	yes	no	Intern.		new x-ray dept.	no disp.	yes	751 includes Gen.		
8	none																						
9		in Gen. Hosp.	yes	yes		?		yes		no		yes	no	no	no			yes	no	yes	170	0	0
10	No Reply																						
11		yes	4	yes		yes	80	yes	120	no		yes	yes	yes	no			yes	yes	yes, if patient is in hosp.	533	14	0
12		yes	1	yes		yes	100		peak kilo volts	no		yes	as nec.	no	no			yes			?	?	?
14		no																no					

TABLE VIII—CONTINUED

15	no																					
16	no																for this work		yes			
17	no												brought in if nec.									
18		yes	2	yes	any			yes	140,-000	no		yes	yes	yes	no			no deep rad. equip.	yes	no	37,072	1,081	0
19		yes	4	yes		yes	100	radio-ther.	90–140	no		yes	yes	yes			con-fer-ences	yes	yes	no			
20		yes	1 half time	yes		no		yes	70 kilo volts 4 mps.	no		yes	no	no	no	no	no	yes	no	no	500	25	0
21	no																						
22	no																	no isola-tion beds, etc.		yes serums			
23		yes	yes	yes		yes	500	yes	130	yes	250	yes	yes	yes	no			yes	yes	yes	33,316	434	1167
24		yes	3	yes		yes	500	yes	100 kv	yes	200 kv	yes	yes	yes	no		Fluor-osc. &GU Rad.	yes	main x-ray, not conta-gious	yes limita-tion	600	occa-sion-ally	none
31	no																						
32	no																						
33	no																						
35	no																						

General.—There is a director in charge of laboratory work in 15 hospitals. In 2 the work is done by the state laboratory; in 2 others by the city laboratory. Only 9 have a full-time director in charge of laboratory work.

Pathological.—Six hospitals have a full-time director of the pathologic laboratory. Often the contagious work is also a responsibility of the pathological laboratory of a general hospital. Seven have part-time directors, and 6 have no director. Only 12 hospitals replied to the question concerning technicians. Among these all but 1 have full-time technicians. Internes work in the pathologic laboratory in only 4 instances, and these duties are of a routine or emergency nature. Among 15 which replied, 2 consider their facilities inadequate, and among 16 replying 10 have facilities for research.

Clinical.—Ten hospitals have full-time directors, and in 12 there are full-time technicians. Internes do laboratory work in 9 instances. It is usually of a routine nature. Blood chemistry work is available in 12 hospitals. In 3 it is not, and the remainder do not reply. Six have "fume hoods," 9 have colorimeters. Nine are able to do basal metabolism tests. Eight of these use a Sanborn machine. Thirteen consider their facilities adequate; 1 does not; the remainder do not reply. Only eleven have facilities for research work.

Bacteriologic.—Ten hospitals have full-time directors of the bacteriologic laboratory. Nine have part-time directors, the remainder failed to reply. Of 17 which replied, 14 employ full-time technicians. In 5 instances internes do some of the routine laboratory work. In no instance do they perform special work. All of 18 hospitals which replied have incubators, 17 are electric, 1 gas. Fifteen keep animals for experimental purposes, and 12 have facilities for research work.

Serologic.—Among 22 hospitals replying to this section, 14 have full- or part-time directors. In 8 instances there is a full-time director. Eleven have full-time technicians. The internes do work in the serologic laboratory in only 2 hospitals. Wassermanns are done in their own laboratory in 9 hospitals, Kahn tests in 10. Among 15 hospitals which replied, all consider their facilities adequate, and 12 report that they have facilities for research which in 2 instances are limited.

Miscellaneous.—Seven hospitals possess facilities for photography, and 3, for color photography. Motion picture photography is available in 2 instances. An electrocardiograph is available in only 9 hospitals.

Diet Kitchen.—Of 20 hospitals which replied, only 12 have trained dietitians in charge of the diet kitchen. Among these there are several whose training in dietetics seems rather sketchy. In one instance the contagious disease patients' diets seem to be in the hands of "one cook in a general hospital," and in another they are left to the tender mercies of a "maid" whose qualifications are "ordinary cooking." We hope not too ordinary. The dietitian has entire charge of the menu in most instances. Standard special diets are drawn up by the medical personnel in 8 instances, in 7 by cooperation of both dietitian and the physician in charge of the case, and in three by the dietitian.

Social Service.—Of 26 hospitals only 8 have social service departments. All of these have a full-time worker in charge of the department. Among 6 which replied, 4 indicated that the person in charge had had special previous training for that position. Six departments have more than 1 full-time worker. Respective numbers were reported as 2, 5, 7, 7, 10, and 10. In several instances we believe, however, that this department does not exclusively serve the contagious disease section, but functions for a general hospital of which the contagious disease hospital is a part.

Eight hospitals report that patients are investigated. This is done in the hospital by 4, in the home by 3, and both hospital and home by 4. Only 2 investigate all cases at the home, but 7 investigate all special cases at home.

In 5 instances a complete social history is taken on all cases. Two departments accept private pay cases. Social histories are filed with medical records in 5 in-

stances, and an abstract is attached to the bedside notes in 2 instances. Among 10 hospitals which replied, 7 investigate the patient's ability to pay charges.

Among 10 hospitals which replied, 7 arrange for convalescent care, and 7 have institutions available for that care. Four hospitals have available foster homes and use them. Three consider that their facilities for convalescent care are not adequate.

Among 10 hospitals 3 follow-up cases after discharge; 5 do this if necessary. Social service assists in getting patients back for recall in 4 instances. Volunteer workers are used by 3 social service departments. The social service department is supported by hospital funds in 2, and the remainder do not reply.

In no instances is there a special lay committee in charge of the social service department.

General Information (1934).—Table IX reveals the number of cases of the more usual contagious diseases admitted to these hospitals during 1934, together with total deaths and the percentage death rate in all hospitals for each disease. Information was also requested concerning cases of other diseases admitted by the hospitals, but the replies are too diverse and varied to warrant charting.

Table IX reveals several figures of particular interest. For instance the mortality per cent for diphtheria and measles are nearly equal; the rate for pertussis is greater than either of these; and the rate for smallpox was zero, no deaths occurring among 56 cases. One may observe that the death rate for chickenpox is low, 0.67 per cent, but that this low rate is accounted for by 759 cases with no deaths, reported from one hospital alone. If the latter figures are omitted, the death rate in the other hospitals is 2.79 per cent or nearly four times the first figure. A grand total of only 1,762 cases of diphtheria admitted for the year 1934 seems to indicate that prophylactic procedures are gaining headway but need to be considerably more emphasized in the cities of the Middle West. Half of the cases of typhoid fever are reported from one hospital and half of the remaining number are evenly divided between the others. In other words 75 per cent of typhoid fever cases in contagious hospitals were found in three localities, namely, St. Louis, Sioux City, and Detroit. These figures of course do not necessarily mean that 75 per cent of all typhoid fever cases are found in these three localities. The fact that among 108 cases of amebic dysentery, 103 are reported by one hospital is accounted for by the Chicago epidemic. Also 25 of a total of 28 bacillary dysentery cases are reported from St. Paul, Minn.

Among other diseases listed under "miscellaneous" and admitted to these hospitals, we find the most frequent to be venereal disease, erysipelas, poliomyelitis, lethargic encephalitis, encephalitis, undulant fever, Vincent's angina, pneumonia, diphtheria carriers, furunculosis, septicemia, various forms of meningitis, toxic erythema, and streptococcic sore throat. A total number of 119 cases of poliomyelitis were admitted, about half of which were reported from Cleveland, Ohio. One hospital in St. Louis reported 346 cases of encephalitis, the reminder of the recent epidemic there. The mortality rate in that hospital was 22.2 per cent. Among 18 hospitals, 673 cases of erysipelas were admitted. The mortality rate was 13.34 per cent.

COMMENT

There is occasion for almost endless comment as one studies the reports concerning contagious hospitals of Region III. We shall not attempt a detailed discussion here for many conclusions are perfectly clear to anyone who is interested enough to study the detailed report. We merely wish to call attention to the more important facts which this and future reports will illuminate.

There are not many large contagious disease hospitals to be found in this region. We received reports from only nine which would be called large, and all of these, of

TABLE IX

GENERAL INFORMATION (1934)

	DIPHTHERIA		SCARLET FEVER		MEASLES		WHOOPING COUGH		SMALLPOX		CHICKENPOX		EPIDEMIC CEREBROSPINAL MENINGITIS		TYPHOID FEVER		AMEBIC DYSENTERY		BACILLARY DYSENTERY	
	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS	CASES	DEATHS
1	4	1	20	2	5	0	6	0	0	0	1	0	1	0	1	0	2	0	0	0
2	No reply																			
3	225	17	3219	47	54	2	54	4	0	0	10	1	104	21	0	0	103	0	0	0
4	No reply																			
7	1		2		8								? 2*		1	1			2	1
8	16		22	2	13		1				1				1					
9			1		3															
10	29	0	17	0	23	0					2	0								
11	248	21	1931	22	81	3	130	21	0	0	40	1	14	4	21	2	1	0	1	0
12	2		311		1		1				1									
14	10	1	317	3	1	0														
15	17	1	581	7	72	0	598	7			759	0	2	0	17	0	2	0		

TABLE IX—CONT'D

16			20												2					
17	5	1	88	3	5	0	6	2	0	0	4	0	6†	4	20	5	0	0	0	0
18	257	8	102	3	18		16	6			18		7	7						
19	22	1	154	2	17	0	33	1	9	0	36	0	3	2	4	0			25	2
20	446	18	254	5	673	47	457	23	12	0	63	3			89	14				
21	1	0	1	0																
22	176	5	133	2					26					2						
23	197	22	524	19	171	23	114	33	0	0	34	0	51	30	1	0				
24	105	19	920	15	81	4	108	15	0	0	45	2	16	5	1	0				
31	1																			
32	2	0	113	2	13	0	1	0	1	0	4	0	1‡	1						
33	31	4	2432	9	10	0	18	1	2	0	8	0	7	3						
34	16	1	239	3	1	0			5	0	1	0								
35			18	0					1	0			1	0						
Totals	1762	120	11,419	146	1250	79	1543	113	56	0	1027	7	206	79	158	22	108	0	28	3
Deaths %	6.8		1.27		6.3		7.3		0		0.67		38.3		13.9		0		10.7	

*Epidemic?
†Suspected various types.
‡Not epidemic.

course, are to be found in the larger cities, specifically Chicago, Detroit, St. Paul, Minneapolis, Cincinnati, St. Louis, Denver, Cleveland, and Milwaukee. With the exception of Denver, we have received questionnaires from no more than one hospital in any city irrespective of size, and in most instances that is the only contagious hospital in that municipality. Naturally there is a marked difference in their respective sizes, between an institution located in Chicago, which serves several millions of people, and one found in Beloit, Wis., which serves a few thousand. Among the larger hospitals the organization is usually more efficient and complete, in reference to staff, laboratory, x-ray facilities, social service, and nursing services. This is to be expected, for smaller institutions cannot afford such a complete organization when their admission volume is relatively low. There are probably certain periods during the year in which there are no patients in many of the smaller institutions.

Nine hospitals are sufficiently large to have house staffs consisting of more than one physician. They employ resident physicians as well as internes and 5 have residents, assistant residents, and internes. Training requirements for these positions seem satisfactory in most instances, save 1 in which senior medical students are employed.

The contagious disease hospital is connected with a medical school or affords training to medical students or both in the following cities: Denver, Evanston, Ill., Detroit, Minneapolis, St. Paul, Cincinnati, Cleveland, St. Louis, and Chicago. Research work is practically limited to the larger hospitals. In 11 instances the hospitals have affiliations that afford training in contagious disease nursing. Some of the courses are too short to be of much value, but others are long enough to be invaluable. The number of nurses who contracted contagious diseases while working in any of the hospitals seems to us to be rather small which fact should speak favorably for efficient training in contagious nursing technic.

Some of the hospitals do not indicate that they have an operating room. We wonder what the procedure would be if an emergency operation should be necessary.

We should have liked more information concerning cross-infections in the respective hospitals, but many seemed reticent about giving it. Whether this was because they could not be proud of their record or simply had kept no accurate account of these mishaps, accidents, or whatever one may call them, we do not know.

X-ray facilities in many hospitals seem excellent; however, we were somewhat startled to discover that 11 report that there are no x-ray facilities. These again are quite small institutions, usually tax supported and the need for x-ray work is probably very infrequent, the consequent conclusion being that cost is too great to warrant the expenditure required when the need is not great. Similar situations are found in reference to various laboratory facilities and services. Although provisions for an efficient organization in all of these facilities in each hospital would appear to be and would really be a great extravagance in many instances, on the other hand, these services are often indispensable if one is to provide efficient medical care. Where they are not available, the patients' chances of recovery may often be seriously impaired. Private patients in these institutions probably can have almost any type of laboratory service if they are willing to pay for it; we wonder, however, if the free patient may not occasionally suffer because of its lack.

REPORT OF THE TREASURER

Statement of Receipts and Disbursements
June 1, 1935 to May 31, 1936

Balance, June 1, 1935			$ 4,489.72
Receipts:			
Initiation Fees		$ 5,670.50	
Dues		13,470.00	
Exhibits (1935)		1,320.00	
Interest on Bonds		206.25	
Miscellaneous		5.00	$20,671.75
			$25,161.47
Disbursements:			
Office			
Salaries			
Secretary	$5,000.00		
Stenographer	1,560.00		
Office Help	360.00		
	$6,920.00		
Rent	515.00		
Traveling Expense	466.86		
Printing and Stationery	554.72		
Postage	457.80		
Office Supplies and Equipment	102.70		
Insurance (Treasurer's Bond)	62.50		
Telephone and Telegrams	30.88		
Exchange and Tax on checks	51.05		
Miscellaneous	43.11	$ 9,204.62	
Subscriptions to Journal	4,635.00		
Annual Meeting (1935 and 1936)	3,157.01		
Purchase of Bonds—Bal. Payment	347.75		
Executive Board Meeting	665.38		
State Expense	389.03	$ 9,194.17	
Regional Expense:			
Region I	307.79		
Certificates	148.80		
II	49.45		
Certificates	80.80		
III	106.68		
Certificates	123.60		
IV	13.18		
Certificates	34.00		
II and III Meeting	134.85	$ 999.15	
Committees:			
Council on Pediatric Research	480.17		
Clinical Investigation and Scientific Research	96.50		
Hospital and Dispensaries	54.00	$ 630.67	$20,028.61
Balance, May 31, 1936			$ 5,132.86

Academy News

Dr. Francis Scott Smyth, of San Francisco, Calif., and Dr. Oscar M. Schloss, of New York City, have recently been made Fellows of the Academy.

Dr. William L. Buhrman of Chicago died on June 10, 1936.

News and Notes

The following men have been certified by the **American Board of Pediatrics** since the last report. The Board again desires to call attention to the increase of the fee to $30, effective Sept. 30, 1936.

Edward Saunders Babcock, Sacramento, Calif.
Edward Parsons Bagg, Holyoke, Mass.
Charles Williams Bailey, Spartanburg, S. C.
Wilford W. Barber, Denver, Colo.
F. Duncan Barnes, New Rochelle, N. Y.
B. J. Berger, Dallas, Texas
Joseph Brown Bilderback, Portland, Ore.
Frank Lee Bivings, Atlanta, Ga.
Crawford Bost, San Francisco, Calif.
Ralph Bowen, Oklahoma City, Okla.
Howard Wheaton Brayton, Hartford, Conn.
Leroy J. Butler, Winston-Salem, N. C.
Dever Smith Byard, New York, N. Y.
John Caffey, New York, N. Y.
Ernest R. Carlo, Fort Wayne, Ind.
Thomas F. Daniels, Baltimore, Md.
John Hart Davis, Cleveland, Ohio
Laurence Richard DeBuys, New Orleans, La.
Katharine Dodd, Nashville, Tenn.
Karl Wilhelm Ebeling, Baltimore, Md.
Ten Eyck Elmendorf, New York, N. Y.
Theodore O. Elterich, Pittsburgh, Pa.
Joseph Wm. Epstein, Cleveland, Ohio
Arthur L. Esserman, Denver, Colo.
Yates W. Faison, Charlotte, N. C.
William White Falkener, Newport News, Va.
Warren Conrad Fargo, Cleveland, Ohio
Lloyd King Felter, Cincinnati, Ohio
Edmund Boyd FitzGerald, Wollaston, Mass.
Morris Friedson, New York, N. Y.
Elias Freidus, Long Beach, N. Y.
Irving A. Frisch, New York, N. Y.
Thomas Bolling Gay, Atlanta, Ga.
John E. Gonce, Jr., Madison, Wis.
Julian Graubarth, New Orleans, La.
William Russell Graves, Memphis, Tenn.
Otto Grob, Detroit, Mich.
Bengt Hamilton, Chicago, Ill.
Ernest W. Hancock, Lincoln, Neb.
Arild Edsten Hansen, Minneapolis, Minn.
Joseph Linn Hetzel, Waterbury, Conn.
John William Holmes, Philadelphia, Pa.
Arthur G. Jacobs, Memphis, Tenn.
Lawrence R. Jacobus, Oakland, Calif.
Herman M. Jahr, Omaha, Neb.
Charles Kimball Johnson, Burlington, Vt.
William Wiley Jones, Denver, Colo.
Gustav Leonard Kaufmann, Chicago, Ill.
Samuel Eleazer Kohn, Milwaukee, Wis.
Edmund Griffin Lawler, Chicago, Ill.
J. Hugh Lewis, Wyandotte, Mich.
Harry L. F. Locke, Hartford, Conn.
Maud Loeber, New Orleans, La.
Walter D. Ludlum, Brooklyn, N. Y.
Robert A. Lyon, Cincinnati, Ohio.
Roderick J. McDonald, Jr., Denver, Colo.
Eugene T. McEnery, Chicago, Ill.

Rustin McIntosh, New York, N. Y.
Walter Caraway McKee, Chicago, Ill.
Edwin Clare McMullen, Pine Bluff, Ark.
Howard B. Mettel, Indianapolis, Ind.
Milo K. Miller, South Bend, Ind.
Louis D. Minsk, Chicago, Ill.
Clyde Moore, Omaha, Neb.
J. Harry Murphy, Omaha, Neb.
Frank C. Neff, Kansas City, Mo.
Samuel Okrent, Cincinnati, Ohio
William J. Orr, Buffalo, N. Y.
Joseph B. Pincus, Brooklyn, N. Y.
Samuel Fitzsimons Ravenel, Greensboro, N. C.
Hartzell Harrison Ray, San Mateo, Calif.
Benjamin B. Rittenberg, Philadelphia, Pa.
Robert Rosenthal, St. Paul, Minn.
Solomon H. Rubin, Boston, Mass.
George Richard Russell, Tulsa, Okla.
Albert L. Salomon, Oklahoma City, Okla.
William J. Scott, Detroit, Mich.
John A. Shaw, Fayetteville, N. C.
Floyd Reeves Smith, Pittsfield, Mass.
Joe T. Smith, Knoxville, Tenn.
Henry E. Stafford, Oakland, Calif.
Albert Valentine Stoesser, Minneapolis, Minn.
Lee Edwards Sutton, Jr., Richmond, Va.
Clifford Sweet, Oakland, Calif.
Carl Leonard Thenebe, Hartford, Conn.
Edward Arthur Wagner, Cincinnati, Ohio
Edward Taylor Wakeman, New Haven, Conn.
Alfred Hamlin Washburn, Denver, Colo.
Gustave F. Weinfeld, Ravinia, Ill.
William Weston, Jr., Columbia, S. C.
Herbert B. Wilcox, New York, N. Y.
Edward A. Wishropp, Detroit, Mich.
Charles H. York, Cleveland, Ohio
Stuart Welsh Adler, Albuquerque, N. M.
Ralph L. Cook, St. Louis, Mo.
Max Miles Ginsburg, Denver, Colo.
Aymer Morgan Hill, Grand Rapids, Mich.
Jasper Stewart Hunt, Charlotte, N. C.
W. Eugene Keiter, Kinston, N. C.
Thomas Myers Palmer, Jacksonville, Fla.
Meyer A. Perlstein, Chicago, Ill.
George Edwin Robertson, Omaha, Neb.
Byron Kenneth Rust, Indianapolis, Ind.
Martha Chandley Souter, Indianapolis, Ind.
Edward Lawrence Tuohy, Minneapolis, Minn.
Ralph Henry Verploeg, Denver, Colo.
Morris Greenberg, New York, N. Y.

At the 48th Annual Meeting of the **American Pediatric Society** at Bolton Landing on Lake George, N. Y., Dr. Henry F. Helmholz was elected president for the ensuing year. Dr. Frederic H. Bartlett, of New York City, was elected vice president. Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis, Mo., was reelected secretary and treasurer. Dr. P. C. Jeans, Iowa City, Iowa, was chosen member of council. Dr. Heyworth N. Sanford was reelected recorder-editor. This meeting was held jointly with the **Canadian Society for the Study of Diseases of Children.** Following the meeting of the Societies, exercises were held for the dedication of the Carl Schurz-Abraham Jacobi Memorial Park at Bolton Landing. Bolton Landing was Dr. Jacobi's summer home. The Society had held a meeting at Bolton Landing in 1905 as the guest of Dr. Jacobi. Dr. Herbert Willy Meyer, of New York, showed motion pictures of Dr. Jacobi made at Bolton Landing shortly before his death.

At the annual meeting of the **Section on Pediatrics of the American Medical Association** in Kansas City, the following officers were elected for the ensuing year: chairman, Ralph M. Tyson, Philadelphia; vice chairman, Aldrich C. Crowe, Atlantic City; secretary, Albert D. Kaiser, Rochester, N. Y.

At the meeting of the **Society for Pediatric Research** in Atlantic City, Dr. Francis Scott Smyth, of San Francisco, Calif., was elected president. Dr. A. A. Weech, 3975 Broadway, New York City, was reelected secretary.

The **Virginia Pediatric Society** held its First Clinical Session on Friday morning, May 29, at the Medical College of Virginia, Richmond, Va. The morning session was devoted to a symposium on disorders of the respiratory tract in infancy and childhood. The leaders of this discussion were Dr. William P. McDowell, Dr. Samuel R. Newman, Dr. Frank D. Wilson, and Dr. W. B. McIlwane. Dr. A. C. Broders, clinical professor of pathology, Medical College of Virginia, discussed malignancy in children.

The afternoon session was devoted to a clinical pathological conference with discussion of papers by Dr. Paul Kimmelstiel, associate in pathology, and members of the pediatric staff, Medical College of Virginia.

The next meeting of the Society will be in October, 1936, at Staunton, Va., at the time of the meeting of the **Medical Society of Virginia.** Dr. J. B. Stone, 2042 Park Ave., Richmond, Va., is secretary of the Society.

The **Fourth International Pediatrics Congress** has been postponed and will probably be held the first week in April, 1937, in Rome, Italy.

Attention is again called to the fact that after September, 1936, certification by the **American Board of Pediatrics** will be by examination only. At this time also the fee for certification will be increased to $30. All pediatricians eligible for certification without examination should attend to this important matter at once.

The Journal of Pediatrics

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